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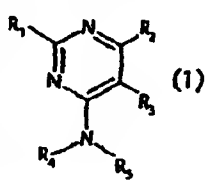
(54) Title: 4-AMINOPYRIMIDINES AND THEIR USE FOR THE ANTIMICROBIAL TREATMENT OF SURFACES



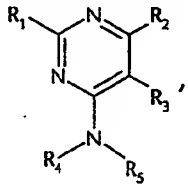
(1)

(57) Abstract: Use of 4-aminopyrimidines of formula (1), wherein R_1, R_2, R_3, R_4 and R_5 are as described in the description in the antimicrobial treatment of surfaces.

4-AMINOPYRIMIDINES AND THEIR USE FOR THE ANTIMICROBIAL TREATMENT OF SURFACES

The present invention relates to substituted 4-aminopyrimidines, to the preparation of such compounds, and to the use of such compounds in the antimicrobial treatment of surfaces, as antimicrobial active substances against gram-positive and gram-negative bacteria, yeasts and fungi and also in the preservation of cosmetics, household products, textiles and plastics and for use in disinfectants.

The present invention relates to the use of 4-aminopyrimidines of formula

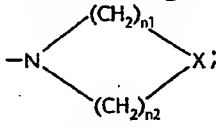
(1)  , wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms; biphenyl or C_6-C_{10}aryl which is unsubstituted or substituted by halogen, C_1-C_5alkyl, C_1-C_5alkoxy or by amino; a 5- to 7-membered heteroaryl radical; or cyclo-C_3-C_7alkyl;

R_3 is hydrogen; phenyl or C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms;

R_4 is hydrogen; C_1-C_{10}alkyl; phenyl; or a 5- to 7-membered heteroaryl radical;

R_5 is C_1-C_{20}alkyl which is unsubstituted or substituted by one or more halogen atoms or by a heterocyclic radical or interrupted by one or more –O- or  groups or by a bivalent heterocyclic radical; NR"R'"-C_1-C_{20}alkyl which is unsubstituted or substituted by a heterocyclic radical or interrupted by one or more –O- or  groups or by a bivalent heterocyclic radical; cyclo-C_5-C_8alkyl; hydroxy-C_1-C_{20}alkyl; phenyl-C_1-C_3alkyl; a heterocyclic radical; or

R_4 and R_5, together with the nitrogen atom linking them, form a radical of formula (1a)  ;

R' is hydrogen; or C_1-C_3alkyl;

R" and R'" are each independently of the other hydrogen; C_1-C_5alkyl; or hydroxy-C_1-C_5alkyl;

X is $>O$; $>CH\text{-}R''''$; or $>N\text{-}R''''$;

R'''' is hydrogen; C_1-C_4alkyl; or heteroaryl-C_1-C_4alkyl; and
n_1 and n_2 are each independently of the other from 1 to 8;
in the antimicrobial treatment of surfaces.

C_1-C_{20}Alkyl radicals are straight-chain or branched alkyl radicals, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, isoamyl or tert-amyl, heptyl, octyl, isooctyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl or eicosyl.

C_3-C_{10}Cycloalkyl denotes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl. Those radicals may be substituted, for example by one or more identical or different C_1-C_4alkyl radicals, especially by methyl, and/or by hydroxy. When cycloalkyl radicals are substituted by one or more substituents, they are substituted preferably by one, two or four, especially by one or two, identical or different substituents.

C_1-C_5Alkoxy radicals are straight-chain or branched radicals such as, for example, methoxy, ethoxy, propoxy, butoxy or pentyloxy.

C_6-C_{10}Aryl and heteroaryl radicals may be unsubstituted or may carry one or more, for example one, two, three or four, identical or different substituents, which may be located in any positions. Examples of such substituents are, for example, C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, trifluoromethyl, cyano, hydroxycarbonyl, C_1-C_4alkoxycarbonyl, aminocarbonyl, amino, C_1-C_4alkylamino, di-C_1-C_4alkylamino and C_1-C_4alkylcarbonylamino.

Heteroaryl radicals are derived from heterocycles containing one, two, three or four identical or different ring hetero atoms, especially from heterocycles containing one, two or three, more especially one or two, identical or different hetero atoms. The heterocycles may be mono- or poly-cyclic, for example mono-, bi- or tri-cyclic. They are preferably mono- or bi-cyclic, especially monocyclic. The rings preferably contain 5, 6 or 7 ring members. Examples of monocyclic and bicyclic heterocyclic systems from which radicals occurring in the

compounds of formula (1) can be derived are, for example, pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, indole, benzothiophene, benzofuran, pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine.

Unsaturated heterocycles may contain, for example, one, two or three unsaturated double bonds in the ring system. 5-membered rings and 6-membered rings in monocyclic and polycyclic heterocycles may also be, especially, aromatic.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

In accordance with the invention, preference is given to the use of compounds of formula (1) wherein

R_5 is $R''R'''N$-C_1-C_{20}alkyl which is uninterrupted or interrupted by one or more –O- or —N(R')— groups or by a bivalent heterocyclic radical;

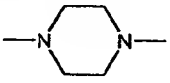
R' is hydrogen; or C_1-C_5alkyl;

R'' and R''' are each independently of the other hydrogen; or methyl;

and

R_1, R_2, R_3 and R_4 are as defined for formula (1).

Very special preference is given to the use of compounds of formula (1) wherein

R_5 is $R''R'''N$-C_1-C_{20}alkyl which is uninterrupted or interrupted by  .

In accordance with the invention, there are furthermore used compounds of formula (1) wherein

R_5 is $R''R'''N$-C_5-C_{20}alkyl which is uninterrupted or interrupted by one or more –O- or —N(R')— groups;

R' is hydrogen; or C_1-C_5alkyl; and

R'' and R''' are each independently of the other hydrogen; or methyl.

Among those compounds, preference is given to those wherein

R_5 is R''R'''N-C_5-C_{20}alkyl; and

R'' and R''' are each independently of the other hydrogen; or methyl.

Very special preference is also given to the use of compounds of formula (1) wherein

R_4 is hydrogen; or C_1-C_5alkyl;

R_5 is C_5-C_{20}alkyl which is unsubstituted or interrupted by –NH-; and

R_1, R_2 and R_3 are as defined for formula (1);

especially compounds of formula (1) wherein

R_1 is hydrogen; C_1-C_5alkyl; unsubstituted or C_1-C_4alkyl-substituted phenyl or phenyl-C_1-C_4alkyl; or pyridino;

R_2 is hydrogen; or C_1-C_5alkyl; especially methyl;

R_3 is hydrogen; or C_1-C_5alkyl;

R_4 is hydrogen; or C_1-C_5alkyl; and

R_5 is C_5-C_{20}alkyl;

and very especially compounds of formula (1) wherein

R_1 is hydrogen; C_1-C_5alkyl, especially isopropyl or methyl; unsubstituted or C_1-C_4alkyl-substituted phenyl; or pyridino;

R_2 is methyl;

R_3 and R_4 are hydrogen; and

R_5 is C_8-C_{18}alkyl.

Among the last-mentioned compounds very special preference is given to the use of those wherein

R_5 is linear C_8-C_{18}alkyl.

Also preferably used are compounds of formula (1) wherein, in formula (1a),

R'''' is hydrogen; or pyridyl-C_1-C_3alkyl; and

n_1 and n_2 are each 2.

Preference is also given to the use of compounds of formula (1) wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl; phenyl which is unsubstituted or substituted by halogen, C_1-C_5alkyl, C_1-C_5alkoxy or by amino; biphenyl; cyclo-C_3-C_7alkyl; 3-pyridyl; 4-pyridyl; 2-thiophenyl; 3-thiophenyl; or thiazolyl;

or compounds of formula (1) wherein

R_3 is hydrogen; or phenyl;

or compounds of formula (1) wherein

R_4 is hydrogen.

Special preference is given to the use of compounds of formula

(2) 

wherein

X is -O-; or  ;

R' is hydrogen; or C_1-C_3alkyl;

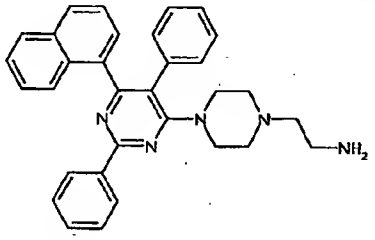
n is 1-3; and

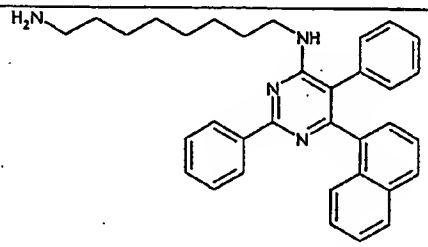
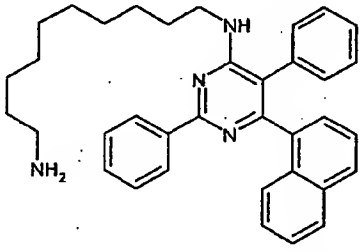
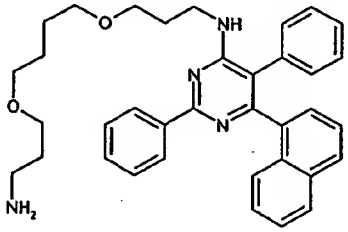
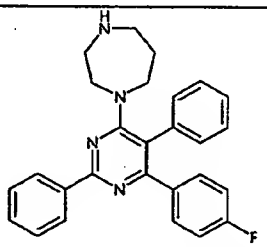
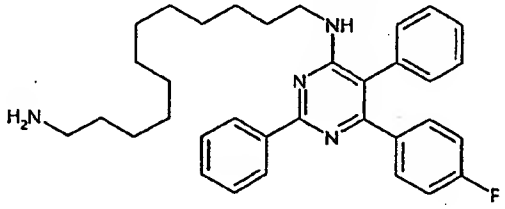
m is 1-3;

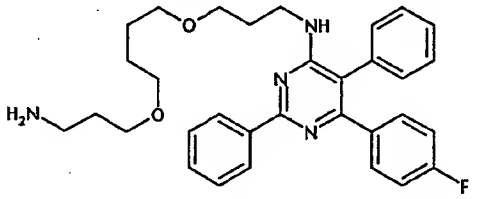
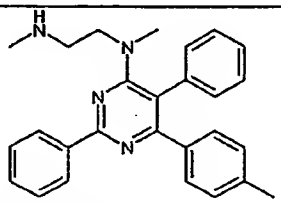
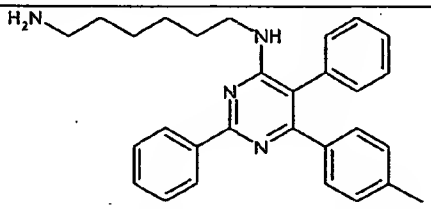
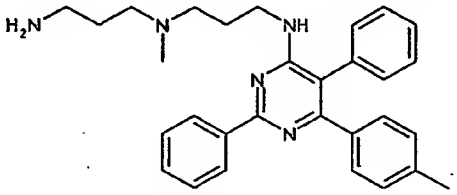
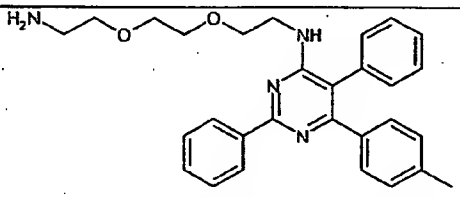
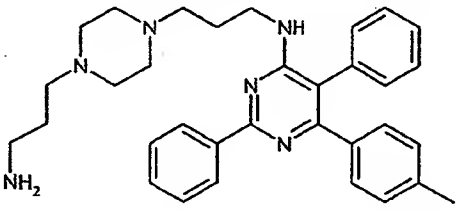
and

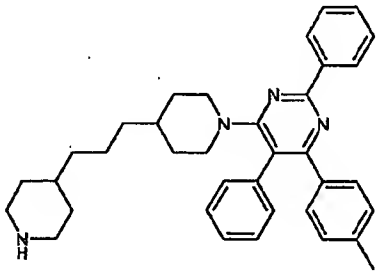
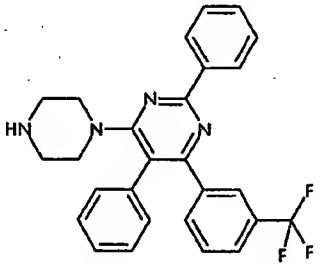
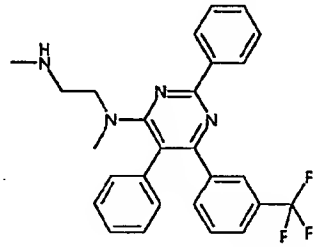
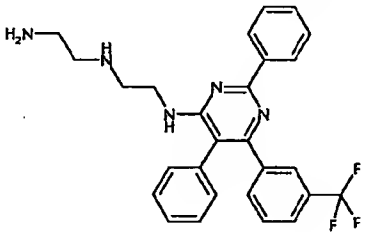
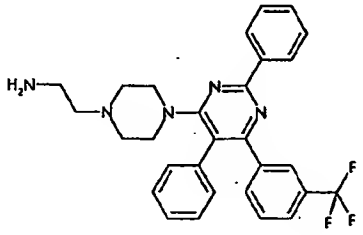
R_1, R_2 and R_3 are as defined for formula 1.

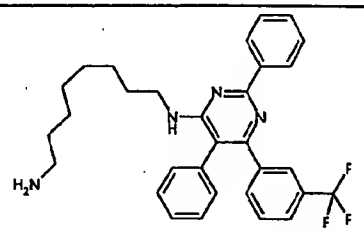
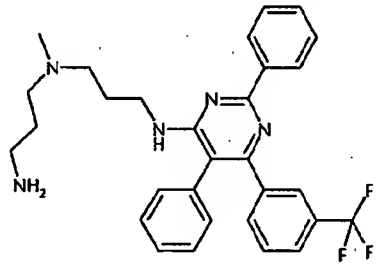
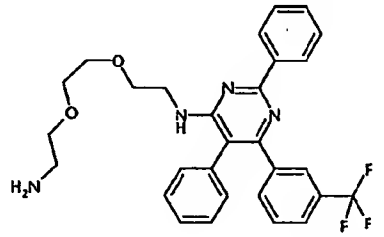
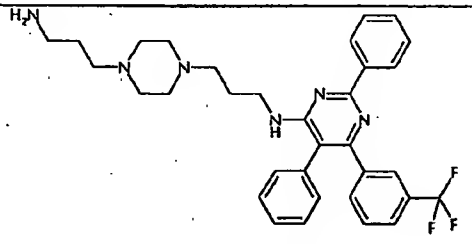
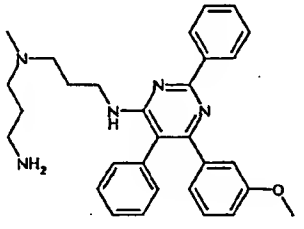
The Table that follows lists, by way of example, further 4-aminopyrimidines according to the invention:

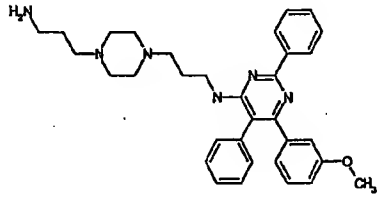
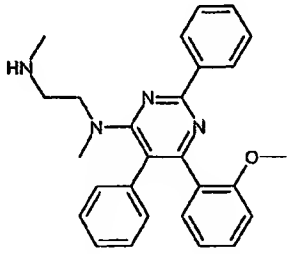
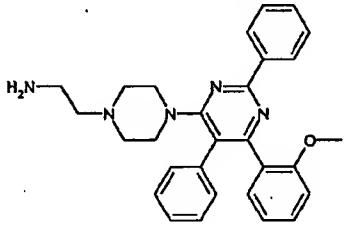
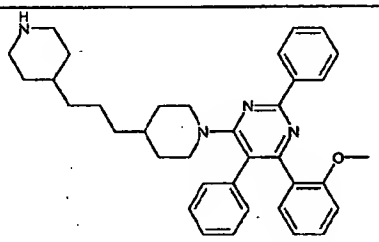
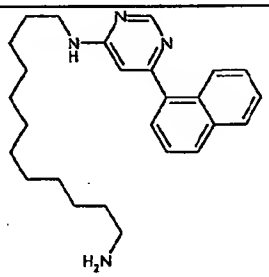
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
3		64	72

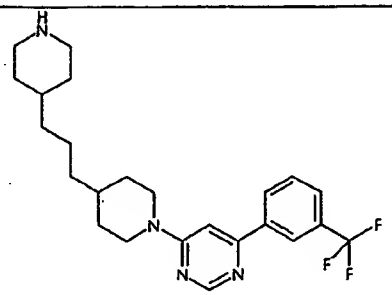
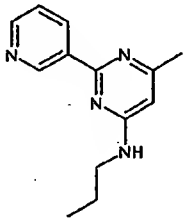
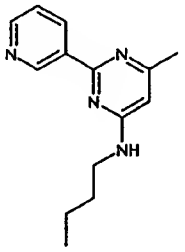
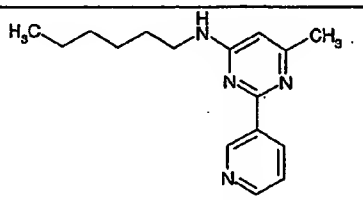
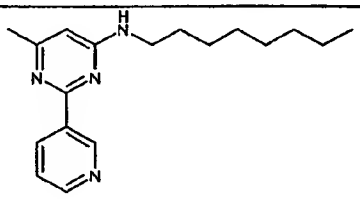
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
4		37	96
5		83	97
6		92	97
7		43	48
8		82	93

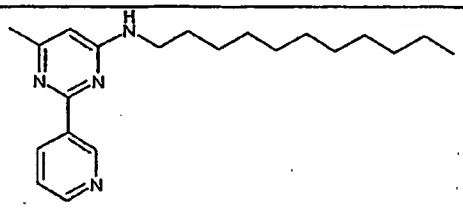
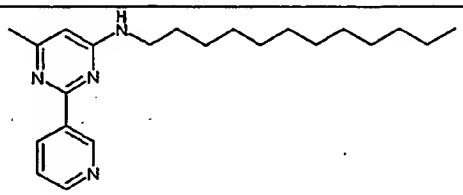
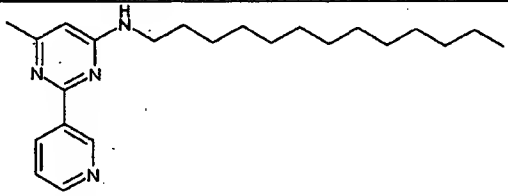
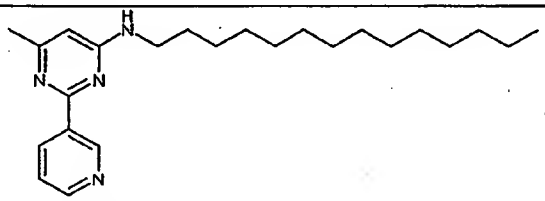
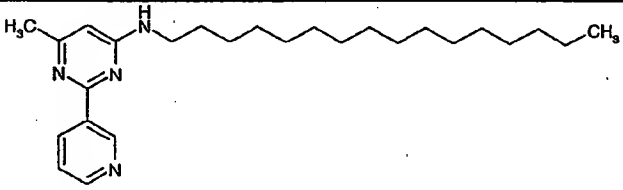
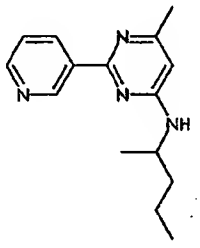
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
9		94	98
10		49	59
11		75	89
12		95	97
13		94	99
14		91	97

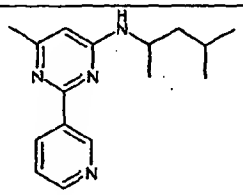
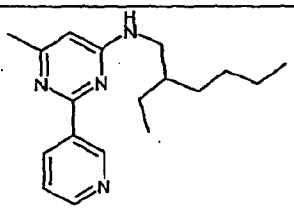
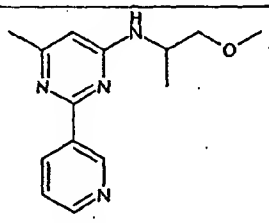
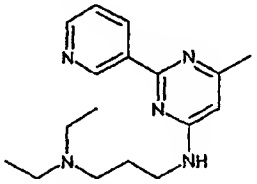
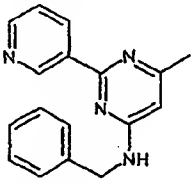
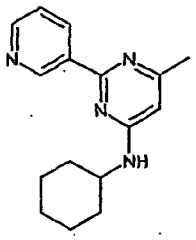
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
15		91	98
16		42	44
17		39	43
18		42	51
19		64	70

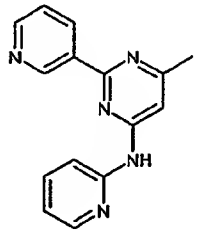
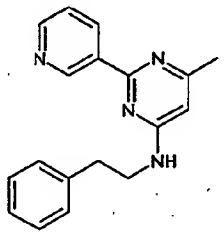
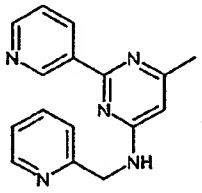
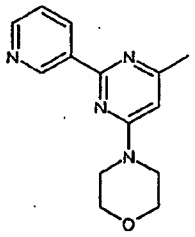
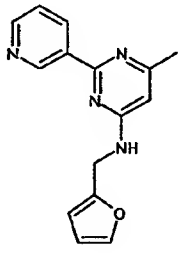
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
20		63	77
21		70	82
22		51	65
23		67	82
24		95	97

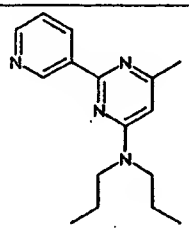
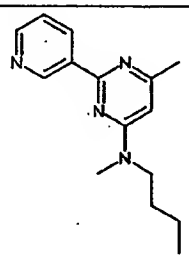
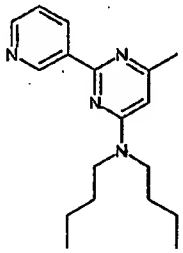
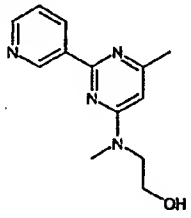
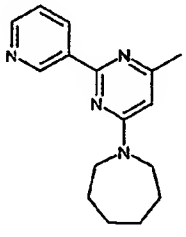
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
25		88	96
26		81	90
27		88	93
28		86	93
29		61	62

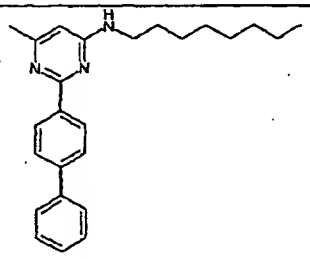
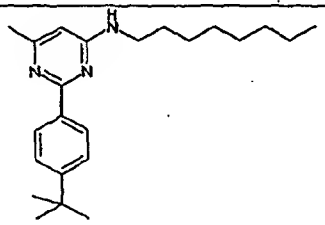
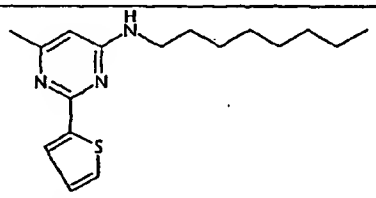
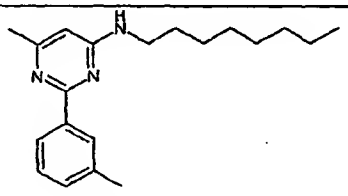
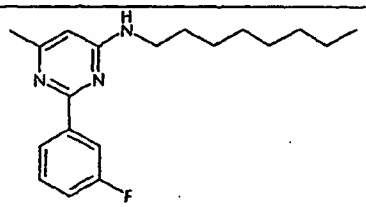
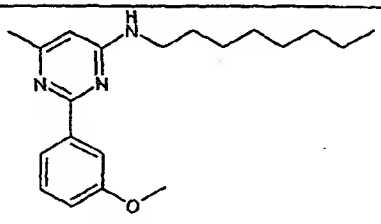
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
30		85	72
31		45	42
32		69	64
33		94	93
34		89	89

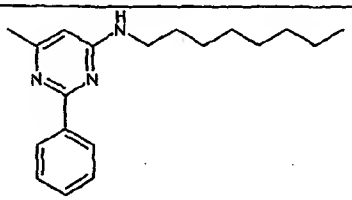
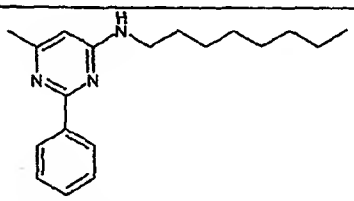
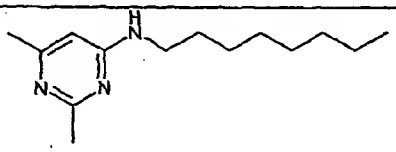
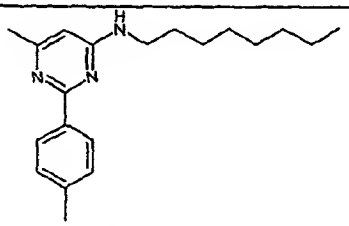
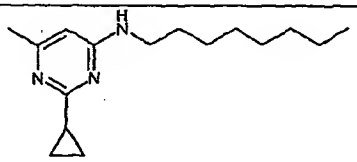
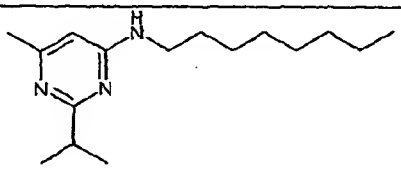
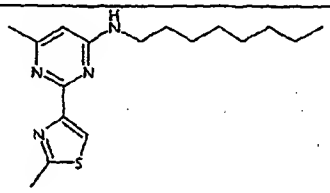
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
35		92	88
36		82	73
37		82	66
38		56	34
39		67	46
40		43	44

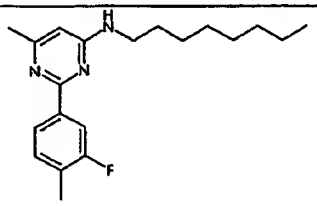
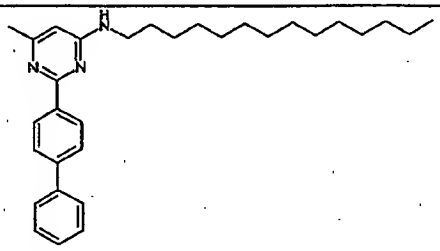
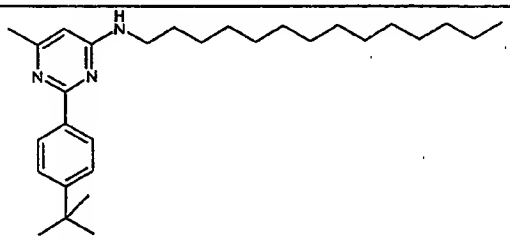
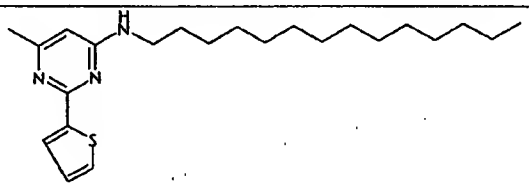
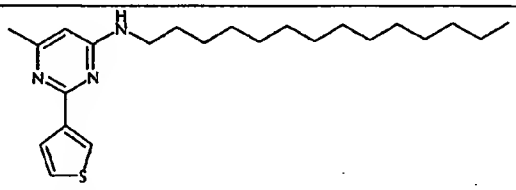
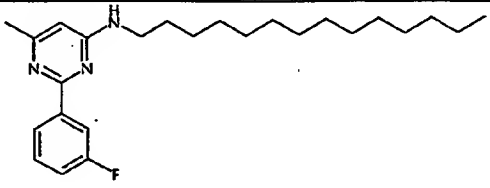
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
41		81	77
42		91	92
43		72	68
44		88	84
45		82	83
46		88	88

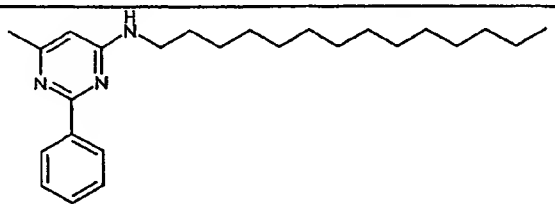
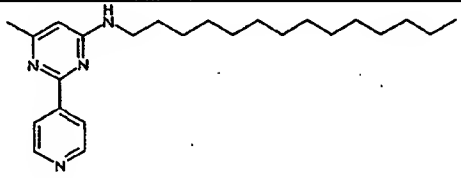
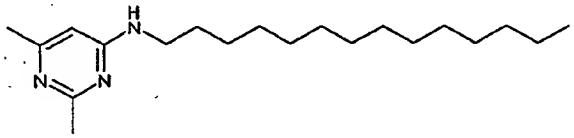
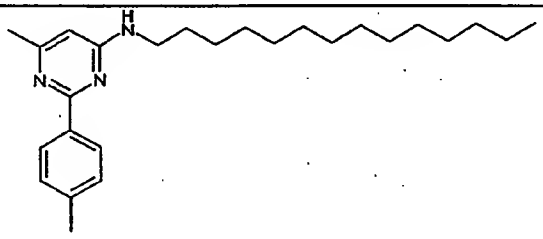
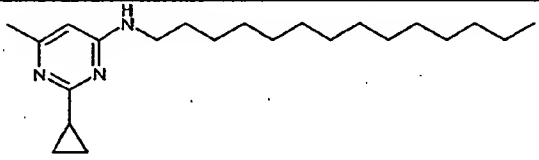
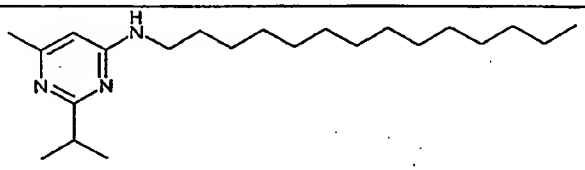
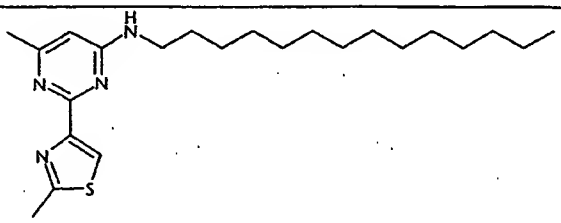
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
47		72	67
48		81	85
49		92	84
50		84	86
51		77	73

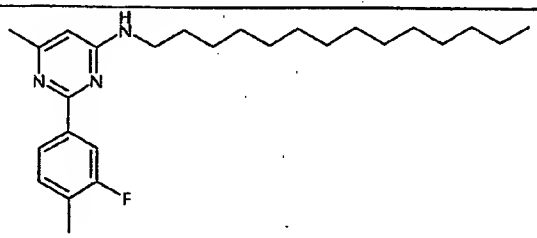
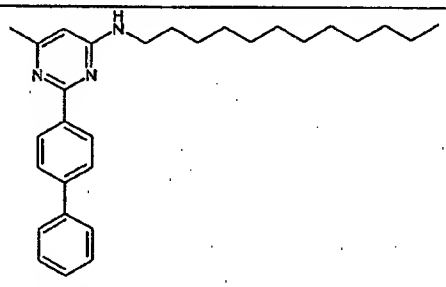
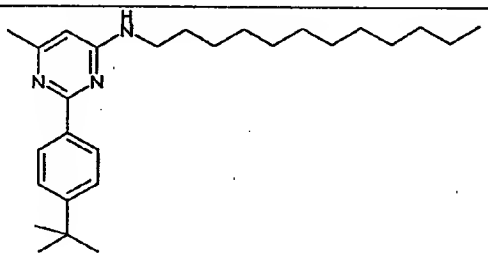
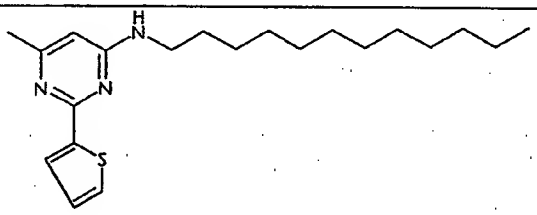
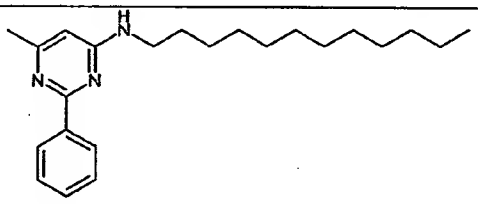
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
52		88	91
53		87	89
54		90	91
55		85	87
56		87	84

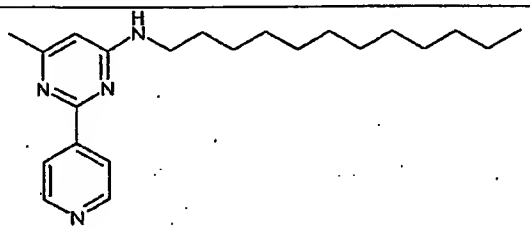
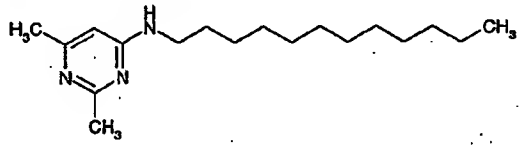
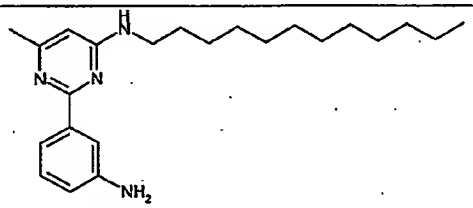
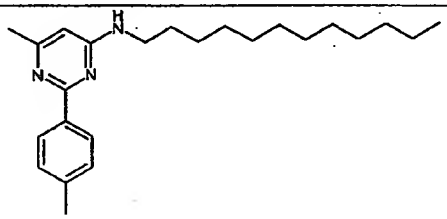
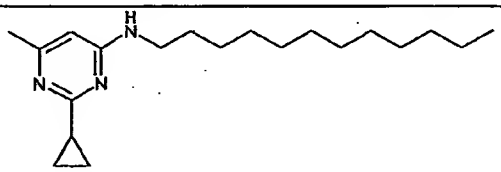
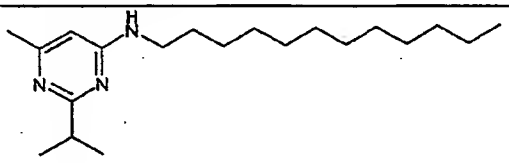
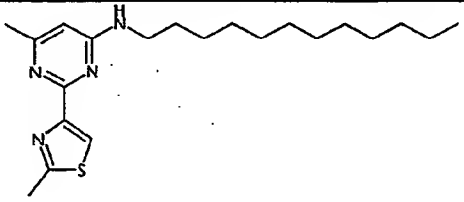
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
57		99	99
58		58	78
59		34	64
60		46	32
61		90	87
62		66	61

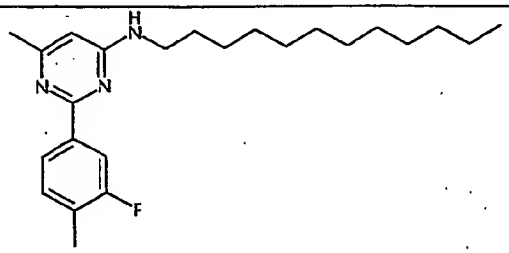
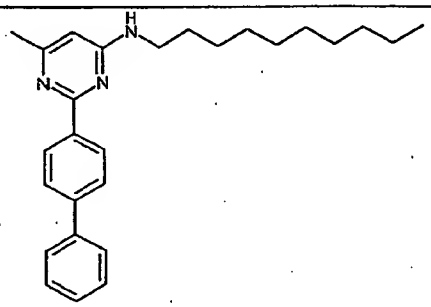
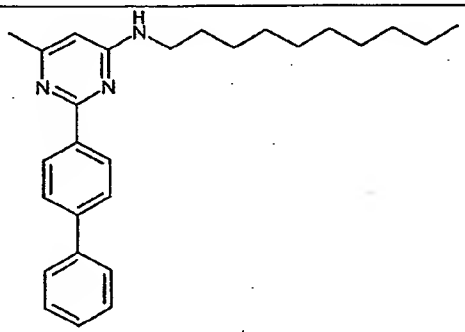
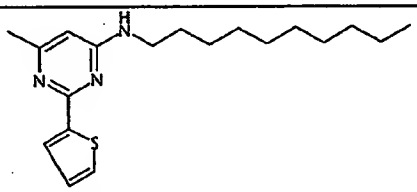
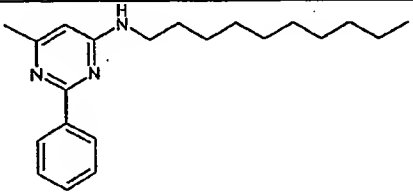
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
63		99	95
64		80	80
65		96	92
66		90	95
67		48	44
68		37	38
69		64	79

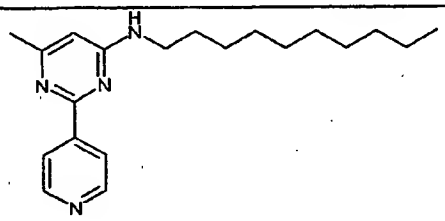
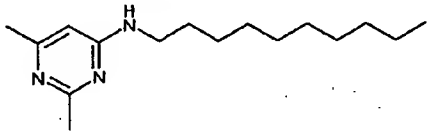
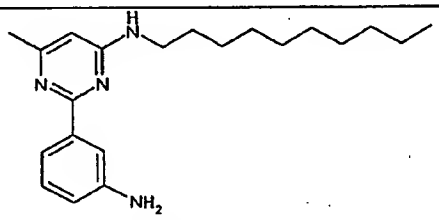
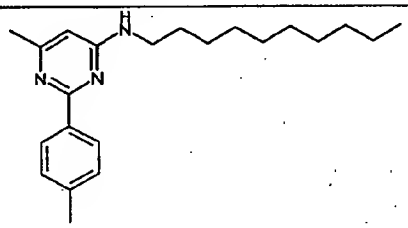
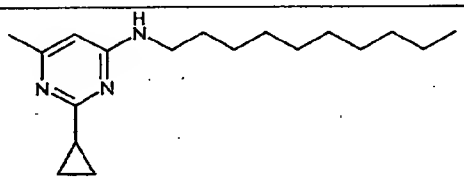
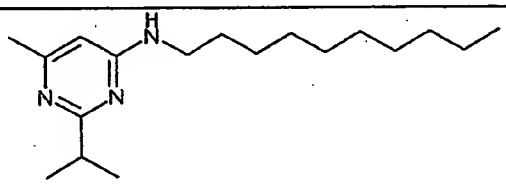
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
70		71	82
71		88	88
72		79	52
73		90	96
74		79	39
75		92	89

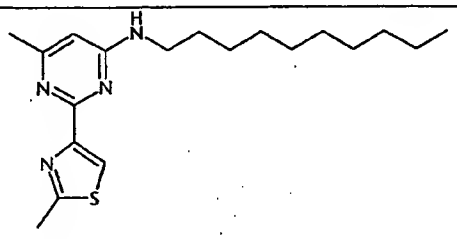
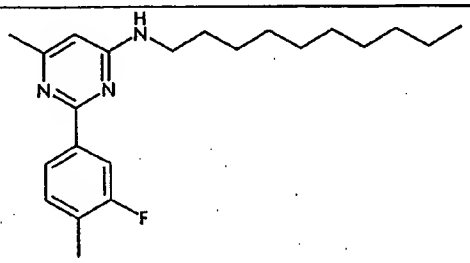
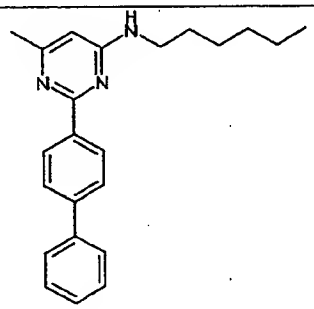
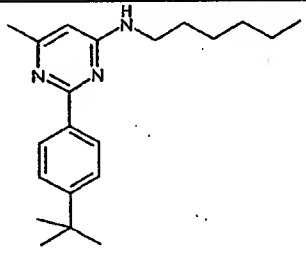
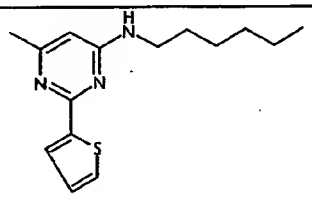
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
76		97	95
77		86	90
78		90	94
79		92	95
80		54	50
81		40	42
82		67	84

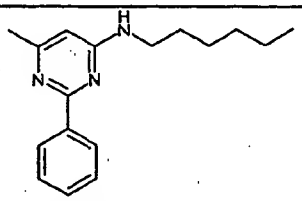
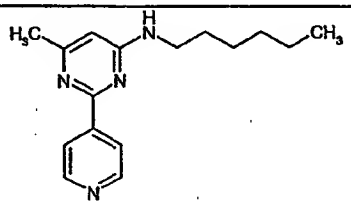
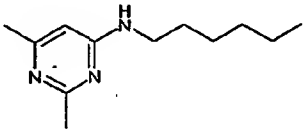
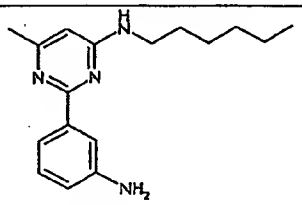
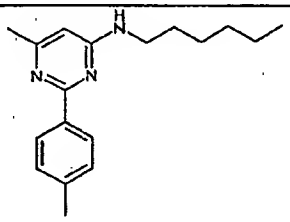
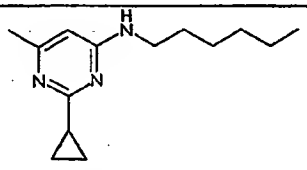
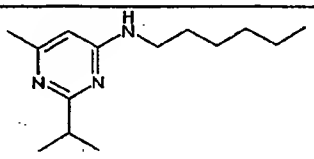
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
83		77	72
84		93	91
85		83	80
86		92	92
87		95	94

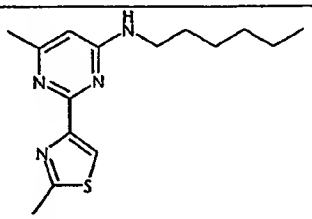
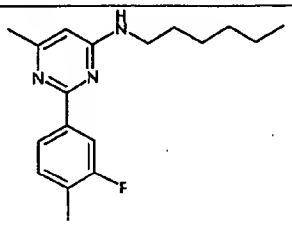
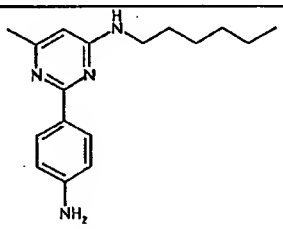
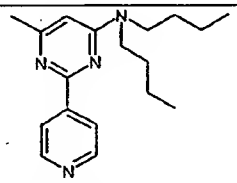
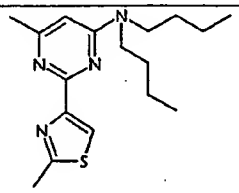
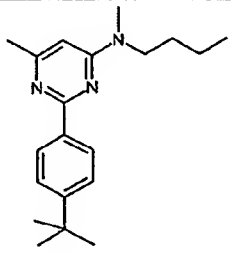
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
88		95	94
89		92	90
90		54	33
91		89	95
92		52	48
93		40	39
94		65	80

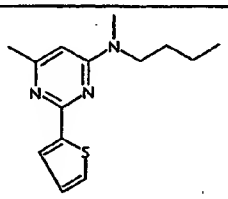
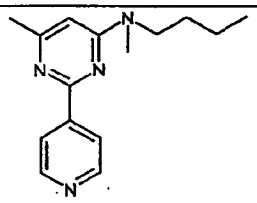
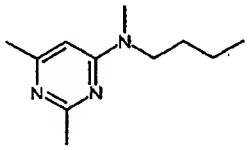
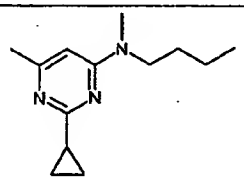
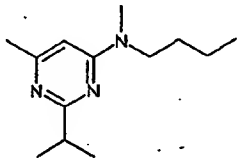
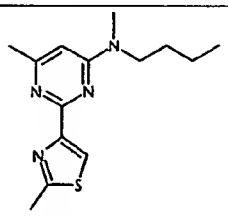
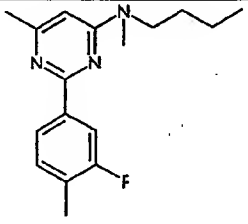
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
95		82	83
96		78	85
97		31	26
98		79	60
99		93	90

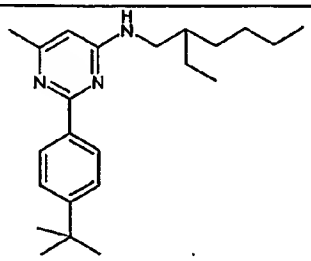
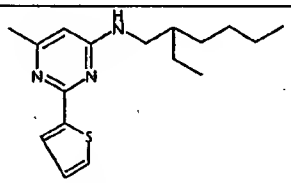
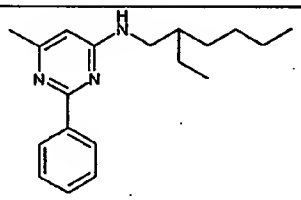
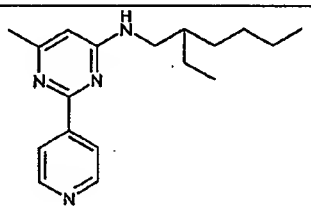
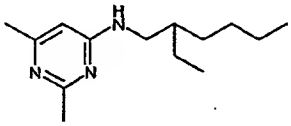
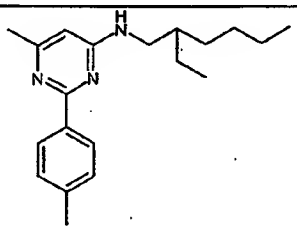
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
100		71	59
101		87	78
102		49	25
103		89	89
104		54	41
105		33	38

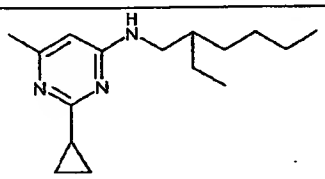
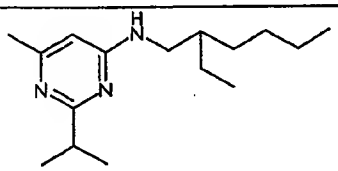
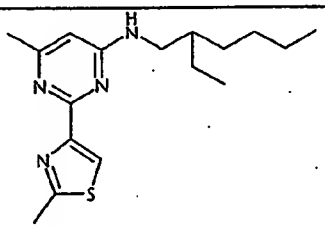
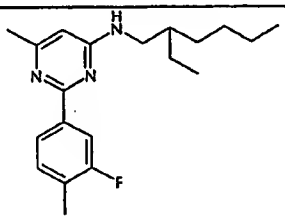
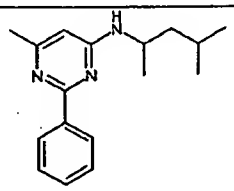
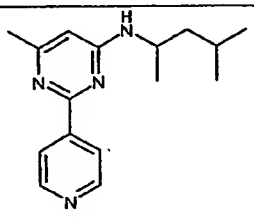
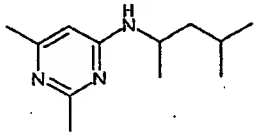
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
106		65	75
107		80	82
108		87	96
109		87	87
110		90	94

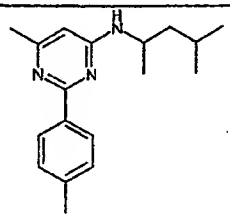
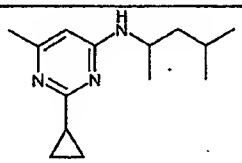
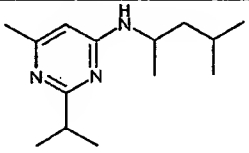
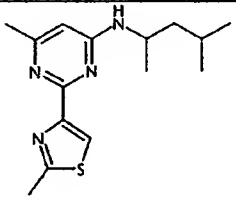
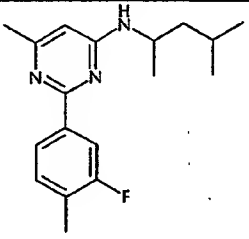
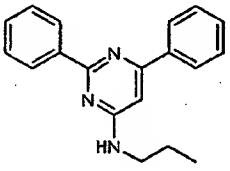
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
111		94	92
112		87	90
113		92	85
114		41	28
115		93	96
116		58	46
117		39	40

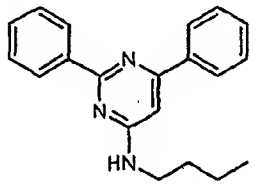
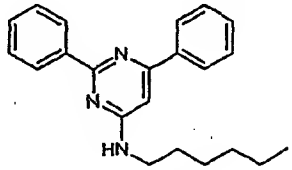
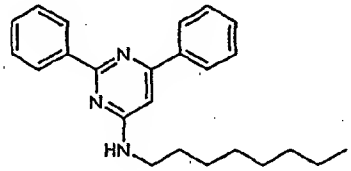
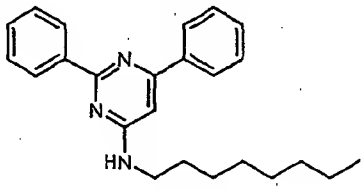
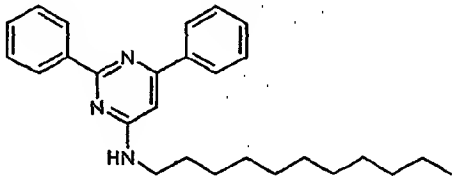
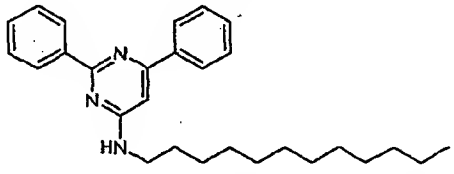
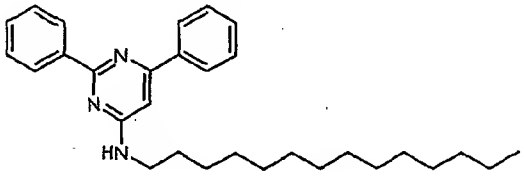
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
118		54	70
119		82	87
120		42	35
121		87	90
122		78	87
123		68	73

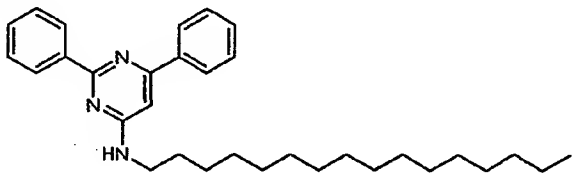
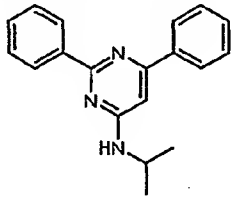
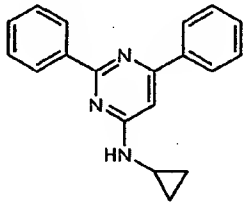
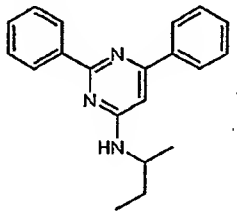
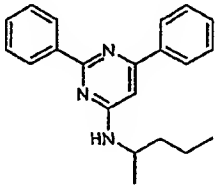
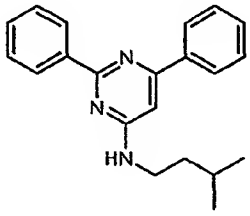
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
124		93	96
125		93	93
126		87	86
127		65	69
128		46	52
129		58	69
130		82	83

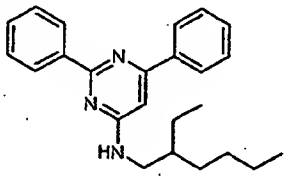
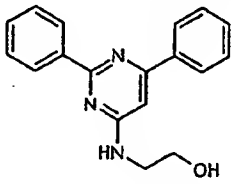
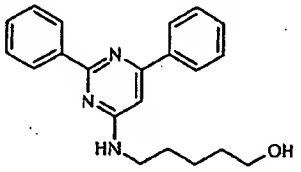
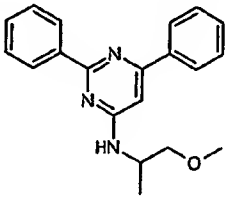
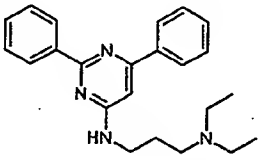
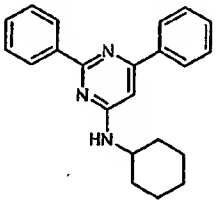
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
131		73	74
132		88	90
133		94	93
134		100	89
135		92	91
136		92	92

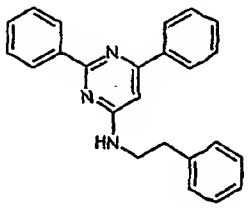
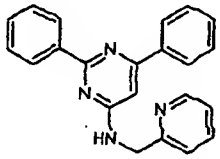
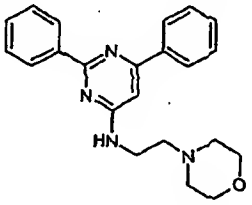
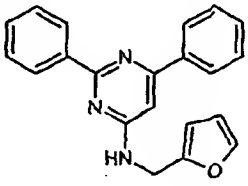
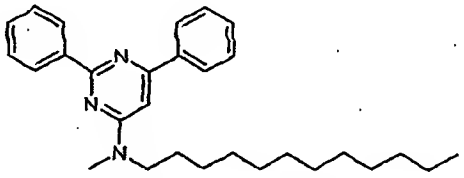
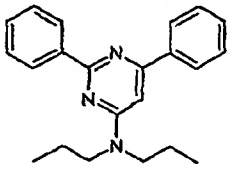
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
137		49	44
138		41	41
139		50	66
140		100	80
141		74	71
142		100	83
143		84	79

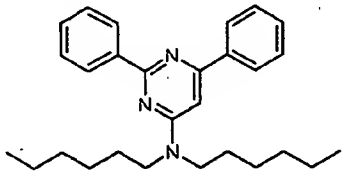
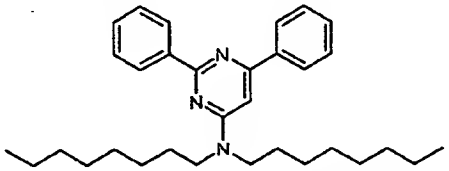
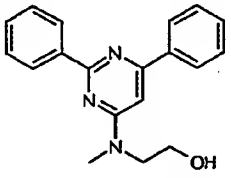
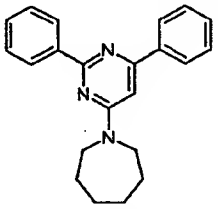
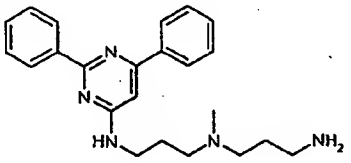
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
144		62	54
145		43	39
146		34	35
147		61	73
148		72	70
149		91	89

Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
150		87	88
151		88	86
152		91	83
153		89	85
154		94	85
155		85	81
156		86	82

Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
157		62	63
158		86	92
159		89	91
160		88	92
161		87	92
162		67	88

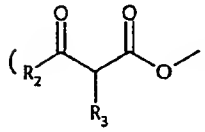
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
163		67	66
164		85	92
165		81	92
166		68	75
167		92	89
168		72	73

Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
169		87	83
170		77	85
171		86	81
172		87	72
173		69	67
174		66	87

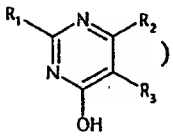
Comp. of formula	Structural formula	Purity [%] 254 nm	Purity [%] 280 nm
175		69	64
176		82	57
177		87	92
178		77	69
179		77	85

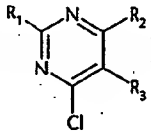
The 4-aminopyrimidines used in accordance with the invention are prepared by methods known *per se* (J. Org. Chem.; 1967, *32*, 1591). For that purpose, a cyano compound (R_1-C≡N) is reacted, in a suitable solvent such as, for example, methanol, ethanol, isopropanol, DMF, tetrahydrofuran etc., with ammonium acetate or ammonium chloride at a temperature of from -10°C to 100°C over a period of from 1 hour to 24 hours to form the corresponding amidine compound ().

The amidine compound is then condensed with an appropriate β-keto ester

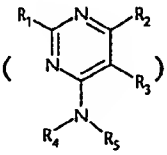
() using an auxiliary base such as, for example, sodium carbonate,

potassium hydroxide, sodium ethanolate, sodium methanolate, potassium tert-butanolate etc., in a suitable solvent such as, for example, methanol, ethanol, butanol, tert-butanol, THF, DMF, acetonitrile, toluene, xylene etc., over a period of from 1 to 24 hours at a temperature of from 40 to 120°C.

The 4-hydroxy-2-pyrimidine compound () thereby obtained is then converted

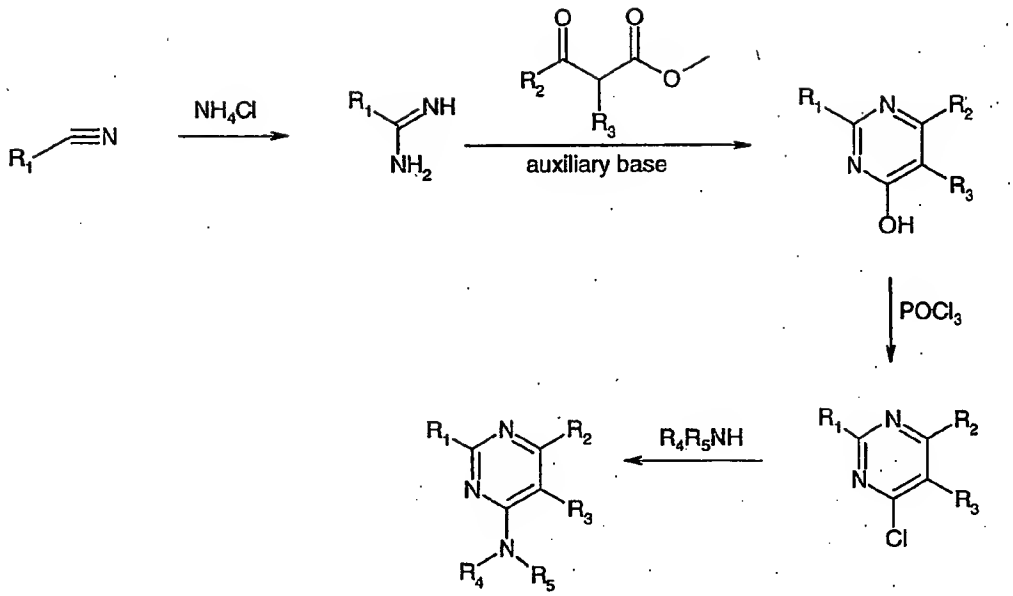
into the corresponding 4-chloro-2-pyrimidine compound () by conventional

methods using phosphorus oxychloride.

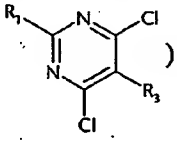
The substituted 4-aminopyrimidines () are obtained by reacting the 4-chloro-2-

pyrimidine compound with a primary or secondary amine (R_4R_5NH) in a suitable solvent such as, for example, DMF, dioxane, toluene, xylene, ethanol, butanol, and an auxiliary base such as, for example, triethylamine, DIEA, sodium carbonate, potassium hydroxide etc., or using an excess of amine at from 40 to 130°C over a period of from 1 to 24 hours.

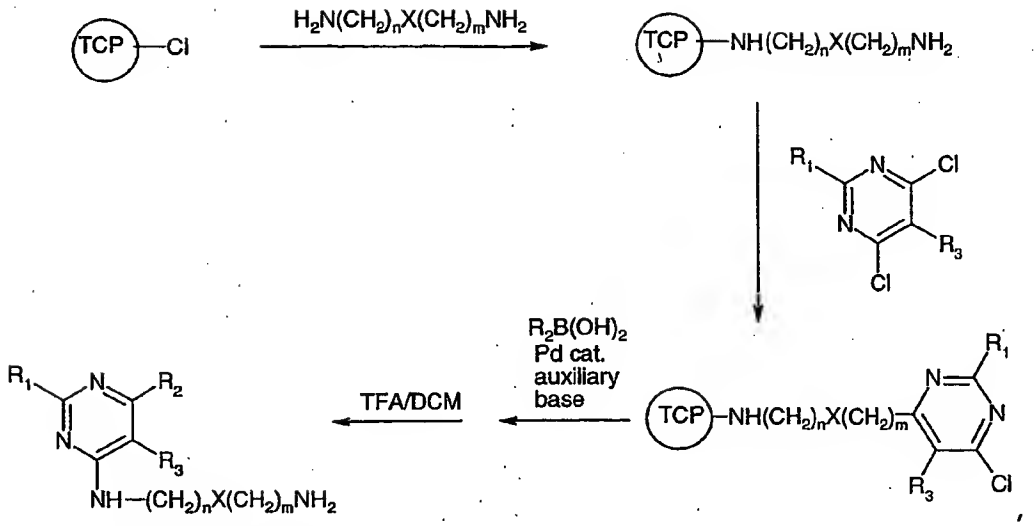
The entire reaction proceeds according to the following scheme:



R_1, R_2, R_3, R_4 and R_5 being as defined for formula (1).

Preparation of the compounds of formula (2) is carried out by reacting an excess of from 2 to 10 equivalents of the diamine compound $H_2N(CH_2)_nX(CH_2)_mNH_2$ in, for example, DMF, dichloromethane, THF or dioxane with trityl chloride polystyrene resin at a temperature of from 10 to 50°C over a period of from 0.5 to 24 hours. From 2 to 10 equivalents of the appropriately substituted 4,6-dichloropyrimidines () are then reacted, in a suitable solvent such as, for example, dichloromethane, DMF, THF or toluene, with the polymer-bound diamines at from 10 to 120°C over a period of from 2 to 48 hours. The 4-chloropyrimidines are reacted with from 2 to 10 equivalents of various boronic acids, from 1 to 10 % of palladium catalyst and from 2 to 10 equivalents of auxiliary base such as, for example, $CaCO_3$ and $NaCO_3$, in, for example, THF, DMF or dioxane. After washing the resin to remove the excess, the target compounds are split off using from 1 to 30 % trifluoroacetic acid (TFA) in dichloromethane (DCM) at 25°C over a period of from 1 to 5 hours. For the purpose of further purification, the substances are freeze-dried from *t*BuOH/water 4:1 with from 1 to 10 % HOAc and once from *t*BuOH/water 4:1.

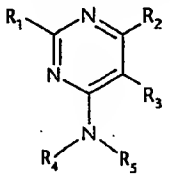
The entire reaction proceeds according to the following scheme:



R_1, R_2, R_3, X, m and n being as defined for formula (2).

Some of the 4-aminopyrimidines used in accordance with the invention are known from the literature and some are novel compounds. The invention relates also to those novel compounds.

The novel compounds correspond to formula

(1')  wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms; biphenyl or C_6-C_{10}aryl which is unsubstituted or substituted by halogen, C_1-C_5alkyl, C_1-C_5alkoxy or by amino; a 5- to 7-membered heteroaryl radical; or cyclo-C_3-C_7alkyl;

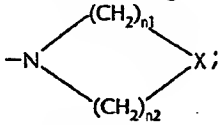
R_3 is hydrogen; phenyl or C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms;

R_4 is hydrogen; C_1-C_{10}alkyl; phenyl; or a 5- to 7-membered heteroaryl radical;

R_5 is C_1-C_{20}alkyl which is unsubstituted or substituted by one or more halogen atoms or by a heterocyclic radical or interrupted by one or more –O- or $-\underset{\underset{R'}{|}}{N}-$ groups or by a

bivalent heterocyclic radical; NR"R'"-C_1-C_{20}alkyl which is unsubstituted or substituted by

a heterocyclic radical or interrupted by one or more –O- or —N(R')— groups or by a bivalent heterocyclic radical; cyclo-C_5-C_8alkyl; hydroxy-C_1-C_{20}alkyl; phenyl-C_1-C_3alkyl; a heterocyclic radical; or

R_4 and R_5, together with the nitrogen atom linking them, form a radical of formula (1a)  ;

R' is hydrogen; or C_1-C_3alkyl;

R'' and R''' are each independently of the other hydrogen; C_1-C_5alkyl; or hydroxy-C_1-C_5alkyl;

X is >O; >CH-R'''' ; or >N-R'''';

R'''' is hydrogen; C_1-C_4alkyl; or heteroaryl-C_1-C_4alkyl; and

n_1 and n_2 are each independently of the other from 1 to 8;

not including compounds of formula (1') wherein simultaneously

R_1 is C_6-C_{10}aryl; or C_1-C_4alkyl; and

R_5 is C_1-C_7alkyl.

The 4-aminopyrimidines used in accordance with the invention exhibit pronounced antimicrobial action, especially against pathogenic gram-positive and gram-negative bacteria and against bacteria of the skin flora, and also against yeasts and moulds. They are accordingly suitable especially for disinfection, deodorisation, and for general and antimicrobial treatment of the skin and mucosa and of integumentary appendages (hair), more especially for the disinfection of hands and wounds.

They are accordingly suitable as antimicrobial active substances and preservatives in personal care preparations such as, for example, shampoos, bath additives, haircare preparations, liquid and solid soaps (based on synthetic surfactants and salts of saturated and/or unsaturated fatty acids), lotions and creams, deodorants, other aqueous or alcoholic solutions, e.g. cleansing solutions for the skin, moist cleaning cloths, oils or powders.

The invention accordingly relates also to a personal care preparation comprising at least one compound of formula (1) and cosmetically tolerable carriers or adjuvants.

The personal care preparation according to the invention contains from 0.01 to 15 % by weight, preferably from 0.1 to 10 % by weight, based on the total weight of the composition, of a compound of formula (1), and cosmetically tolerable adjuvants.

Depending upon the form of the personal care preparation, it comprises, in addition to the 4-aminopyrimidine of formula (1), further constituents such as, for example, sequestering agents, colorants, perfume oils, thickeners or solidifiers (consistency regulators), emollients, UV-absorbers, skin protective agents, antioxidants, additives that improve the mechanical properties, such as dicarboxylic acids and/or aluminium, zinc, calcium or magnesium salts of C_{14}-C_{22}fatty acids, and, optionally, preservatives.

The personal care preparation according to the invention may be in the form of a water-in-oil or oil-in-water emulsion, an alcoholic or alcohol-containing formulation, a vesicular dispersion of an ionic or non-ionic amphiphilic lipid, a gel, a solid stick or an aerosol formulation.

As a water-in-oil or oil-in-water emulsion, the cosmetically tolerable adjuvant contains preferably from 5 to 50 % of an oil phase, from 5 to 20 % of an emulsifier and from 30 to 90 % water. The oil phase may comprise any oil suitable for cosmetic formulations such as, for example, one or more hydrocarbon oils, a wax, a natural oil, a silicone oil, a fatty acid ester or a fatty alcohol. Preferred mono- or poly-ols are ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and sorbitol.

Cosmetic formulations according to the invention are used in various fields. There come into consideration, for example, especially the following preparations:

- skin-care preparations, e.g. skin-washing and cleansing preparations in the form of tablet-form or liquid soaps, synthetic detergents or washing pastes,
- bath preparations, e.g. liquid (foam baths, milks, shower preparations) or solid bath preparations, e.g. bath cubes and bath salts;
- skin-care preparations, e.g. skin emulsions, multi-emulsions or skin oils;
- cosmetic personal care preparations, e.g. facial make-up in the form of day creams or powder creams, face powder (loose or pressed), rouge or cream make-up, eye-care preparations, e.g. eyeshadow preparations, mascaras, eyeliners, eye creams or eye-fix creams; lip-care preparations, e.g. lipsticks, lip gloss, lip contour pencils, nail-care

preparations, such as nail varnish, nail varnish removers, nail hardeners or cuticle removers;

- intimate hygiene preparations, e.g. intimate washing lotions or intimate sprays;
- foot-care preparations, e.g. foot baths, foot powders, foot creams or foot balsams, special deodorants and antiperspirants or callus-removing preparations;
- light-protective preparations, such as sun milks, lotions, creams or oils, sun-blocks or tropicals, pre-tanning preparations or after-sun preparations;
- skin-tanning preparations, e.g. self-tanning creams;
- depigmenting preparations, e.g. preparations for bleaching the skin or skin-lightening preparations;
- insect-repellents, e.g. insect-repellent oils, lotions, sprays or sticks;
- deodorants, such as deodorant sprays, pump-action sprays, deodorant gels, sticks or roll-ons;
- antiperspirants, e.g. antiperspirant sticks, creams or roll-ons;
- preparations for cleansing and caring for blemished skin, e.g. synthetic detergents (solid or liquid), peeling or scrub preparations or peeling masks;
- hair-removal preparations in chemical form (depilation), e.g. hair-removing powders, liquid hair-removing preparations, cream- or paste-form hair-removing preparations, hair-removing preparations in gel form or aerosol foams;
- shaving preparations, e.g. shaving soap, foaming shaving creams, non-foaming shaving creams, foams and gels, preshave preparations for dry shaving, aftershaves or aftershave lotions;
- fragrance preparations, e.g. fragrances (eau de Cologne, eau de toilette, eau de parfum, parfum de toilette, perfume), perfume oils or perfume creams;
- dental care, denture-care and mouth-care preparations, e.g. toothpastes, gel toothpastes, tooth powders, mouthwash concentrates, anti-plaque mouthwashes, denture cleaners or denture fixatives;
- cosmetic hair-treatment preparations, e.g. hair-washing preparations in the form of shampoos and conditioners, hair-care preparations, e.g. pretreatment preparations, hair tonics, styling creams, styling gels, pomades, hair rinses, treatment packs, intensive hair treatments, hair-structuring preparations, e.g. hair-waving preparations for permanent waves (hot wave, mild wave, cold wave), hair-straightening preparations, liquid hair-setting preparations, hair foams, hairsprays, bleaching preparations, e.g. hydrogen peroxide solutions, lightening shampoos, bleaching creams, bleaching powders,

bleaching pastes or oils, temporary, semi-permanent or permanent hair colorants, preparations containing self-oxidising dyes, or natural hair colorants, such as henna or camomile.

An antimicrobial soap has, for example, the following composition:
0.01 to 5 % by weight of a compound of formula (1)
0.3 to 1 % by weight titanium dioxide,
1 to 10 % by weight stearic acid,
soap base ad 100 %, e.g. a sodium salt of tallow fatty acid or coconut fatty acid, or glycerol.

A shampoo has, for example, the following composition:
0.01 to 5 % by weight of a compound of formula (1),
12.0 % by weight sodium laureth-2-sulfate,
4.0 % by weight cocamidopropyl betaine,
3.0 % by weight NaCl and
water ad 100 %.

A deodorant has, for example, the following composition:
0.01 to 5 % by weight of a compound of formula (1),
60 % by weight ethanol,
0.3 % by weight perfume oil, and
water ad 100 %.

The invention relates also to an oral composition containing from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formula (1), and orally tolerable adjuvants.

Example of an oral composition:
10 % by weight sorbitol,
10 % by weight glycerol,
15 % by weight ethanol,
15 % by weight propylene glycol,
0.5 % by weight sodium lauryl sulfate,
0.25 % by weight sodium methylcocyl taurate,

0.25 % by weight polyoxypropylene/polyoxyethylene block copolymer,
0.10 % by weight peppermint flavouring,
0.1 to 0.5 % by weight of a compound of formula (1), and
48.6 % by weight water.

The oral composition according to the invention may be, for example, in the form of a gel, a paste, a cream or an aqueous preparation (mouthwash).

The oral composition according to the invention may also comprise compounds that release fluoride ions which are effective against the formation of caries, for example inorganic fluoride salts, e.g. sodium, potassium, ammonium or calcium fluoride, or organic fluoride salts, e.g. amine fluorides, which are known under the trade name Olafluor.

The 4-aminopyrimidines of formula (1) used in accordance with the invention are also suitable for treating, especially preserving, textile fibre materials. Such materials are undyed and dyed or printed fibre materials, for example of silk, wool, polyamide or polyurethanes, and especially cellulosic fibre materials of all kinds. Such fibre materials are, for example, natural cellulose fibres, such as cotton, linen, jute and hemp, as well as cellulose and regenerated cellulose. Preferred suitable textile fibre materials are made of cotton.

The 4-aminopyrimidines according to the invention are suitable also for treating, especially imparting antimicrobial properties to or preserving, plastics such as, for example, polyethylene, polypropylene, polyurethane, polyester, polyamide, polycarbonate, latex etc.. Fields of use therefor are, for example, floor coverings, plastics coatings, plastics containers and packaging materials; kitchen and bathroom utensils (e.g. brushes, shower curtains, sponges, bathmats), latex, filter materials (air and water filters), plastics articles used in the field of medicine such as, for example, dressing materials, syringes, catheters etc., so-called "medical devices", gloves and mattresses.

Paper, for example papers used for hygiene purposes, may also be provided with antimicrobial properties using the 4-aminopyrimidines according to the invention.

It is also possible for nonwovens such as, for example, nappies/diapers, sanitary towels, panty liners, and cloths for hygiene and household uses, to be provided with antimicrobial properties in accordance with the invention.

The 4-aminopyrimidines of formula (1) are also used in washing and cleaning formulations such as, for example, liquid or powder washing agents or softeners.

The 4-aminopyrimidines of formula (1) can also be used especially in household and general-purpose cleaners for cleaning and disinfecting hard surfaces.

A cleaning preparation has, for example, the following composition:
0.01 to 5 % of a compound of formula (1)
3.0 % octyl alcohol 4EO
1.3 % fatty alcohol C_8-C_{10}polyglucoside
3.0 % isopropanol
water ad 100 %.

In addition to preserving cosmetic and household products, the preservation of technical products, the provision of technical products with antimicrobial properties and use as a biocide in technical processes are also possible, for example in paper treatment, especially in paper treatment liquors, printing thickeners of starch or cellulose derivatives, surface-coatings and paints.

The 4-aminopyrimidines of formula (1) are also suitable for the antimicrobial treatment of wood and for the antimicrobial treatment of leather, the preserving of leather and the provision of leather with antimicrobial properties.

The compounds according to the invention are also suitable for the protection of cosmetic products and household products from microbial damage.

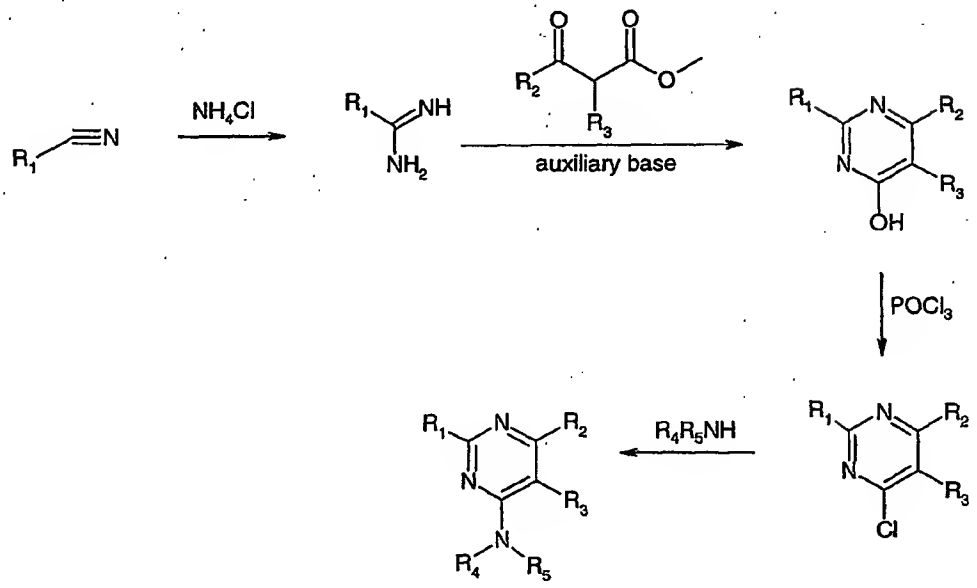
The following Examples illustrate, but do not limit, the present invention.

Implementation Examples:

General work procedure for parallel synthesis of 4-aminopyrimidines:

Example 1:

Reaction Scheme



Preparation of 4-chloro-6-methyl-2-phenylpyrimidine

2.2 g of benzamidine hydrochloride (14.05 mmol) are reacted, in 10 ml of absolute EtOH, with 5.43 ml (14.05 mmol) of 20 % sodium ethanolate solution and then condensed with 1.66 g of methyl acetoacetate (14.29 mmol) for 4 hours at 90°C.

The crude product is concentrated by evaporation and taken up in 30 ml of toluene.

4.31 g of phosphorus oxychloride (28.1 mmol) are added and the reaction mixture is heated at 120°C for 3 hours. After cooling to 20°C, the excess is neutralised with sodium hydroxide solution, and the mixture is diluted with ethyl acetate and then washed with water and saturated sodium chloride solution.

The product solution is dried over sodium sulfate and concentrated by evaporation.

2.2 g of 4-chloro-6-methyl-2-phenylpyrimidine (77.7 % of theory) are obtained.

Example 2: Reaction of 4-chloro-6-methyl-2-phenylpyrimidine with monoamines

20.5 mg of 4-chloro-6-methyl-2-phenylpyrimidine (0.1 mmol) are heated with 3 equivalents of monoamines (0.3 mmol) in 0.5 ml of absolute dioxane at 100°C for 20 hours. After cooling, the products are concentrated *in vacuo*, taken up in t-BuOH/water 4/1 and freeze-dried. The end products are analysed by LC-MS.

Example 3: Loading of trityl chloride polystyrene resin with N,N-bis(3-aminopropyl)methyl-amines and reaction with 4,6-dichloro-2,5-diphenylpyrimidine

In each case, 50 mg of resin (1.29 mmol/g) are shaken in 1 ml of DMF with 94 mg of N,N-bis(3-aminopropyl)methylamine (0.645 mmol) at 25°C for 3 hours. The resin is filtered off and washed with DCM, MeOH, THF, MeOH and DCM and dried *in vacuo*.

The resin is shaken in 1 ml of DMF with 0.194 g of 4,6-dichloro-2,5-diphenylpyrimidine (0.645 mmol) and 90 µl of triethylamine (0.645 mmol) at 25°C for 3 hours.

The resin is filtered off and washed with DCM, MeOH, THF, MeOH, DCM and MeOH and dried *in vacuo*.

Example 4: Parallel reaction of 4-amino-6-chloro-1,5-diphenylpyrimidine-TCP resins with various boronic acids and splitting off

The resin is heated with 126.1 g of caesium carbonate (6 eq., 0.387 mmol) and 300 µl of a toluene solution of 0.1 eq. of a palladium catalyst (WO 01/16057) at 95°C for 15 minutes. After adding 3 eq. of a boronic acid, dissolved in 700 µl of toluene solution, the mixture is heated at 90°C for 1 hour.

After cooling, the resin is filtered off and washed with DMF, MeOH, THF, MeOH and DCM and dried *in vacuo*.

The products are split off using 1.5 ml of a 5 % TFA/DCM solution at room temperature for 3 hours. The resin is then washed with 1 ml of DCM and 1 ml of MeOH, and the combined solutions are concentrated to dryness by evaporation. The end products are analysed by LC-MS.

Example 5: Preparation of 4-chloro-6-methyl-2-tolylpyrimidine

2.5 g of 4-methyl-benzamidine hydrochloride (14.65 mmol) are reacted in 10 ml of absolute EtOH with 5.66 ml of a 20 % solution of sodium ethanolate (14.65 mmol) and then condensed with 1.73 g of methyl acetoacetate (14.88 mmol) at 90°C for 4 hours. The crude product is concentrated by evaporation and taken up in 30 ml of toluene. 6.74 g of

phosphorus oxychloride (44.0 mmol) are added and the reaction mixture is heated at 120°C for 3 hours. After cooling to 20°C, the excess is neutralised with sodium hydroxide solution, and the mixture is diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution and then with water. The product solution is concentrated by evaporation and separated by column chromatography (hexane/EE: 5/1). 2.1 g of 4-chloro-6-methyl-2-tolylpyrimidine (66.5 % of theory) are obtained.
NMR: 1H (ppm in DMSO): 2.4,s,3H; 2.55,s,3H; 7.3,d,2H; 7.5,s,1H; 8.25,d,2H

Example 6: Reaction of 4-chloro-6-methyl-2-(4-methyl)-phenylpyrimidine with monoamines
21.9 mg of 4-chloro-6-methyl-2-(4-methyl)-phenylpyrimidine (0.1 mmol) are heated with 3 eq. of monoamines (0.3 mmol) in 0.5 ml of absolute dioxane at 100°C for 20 hours. After cooling, the products are concentrated *in vacuo*, taken up in t-BuOH/water 4/1 and freeze-dried. The end products are analysed by LC-MS.

Example 7: Reaction of 4-chloro-6-methyl-2-(4-methyl)-phenylpyrimidine with octylamine
1.36 g of 4-chloro-6-methyl-2-(4-methyl)-phenylpyrimidine (6.23 mmol) are heated with 886 mg of octylamine (6.85 mmol) and 2.58 g of potassium carbonate (18.68 mmol) in 10 g of dioxane at 100°C for 48 hours. After cooling, the product is taken up in 100 ml of ethyl acetate and washed with sodium hydroxide solution 0.5 mol/l, saturated sodium hydrogen carbonate solution and water. The product is concentrated *in vacuo*, taken up in t-BuOH/water 4/1 and freeze-dried.
1.92 g of 4-chloro-6-methyl-2-(4-methyl)-phenylpyrimidine (6.15 mmol, 98.7 % of theory) are obtained.
The end product is analysed by NMR, GC-MS and GC.
NMR 1H (ppm in DMSO): 0.9,t,3H; 1.25,m,12H; 1.55,m,2H; 2.25,s,3H; 2.3,s,3H; 6.4,s,1H; 7.1,m,1H; 7.2,d,2H; 8.2,d,2H; (m/z = 311);
GC: 95 % purity

Example 8: Preparation of 4-chloro-2-isopropyl-6-methylpyrimidine
76.1 g of 2-isopropyl-6-methyl-4-pyrimidinol [2814-20-2] (500 mmol) are dissolved in 300 ml of toluene at 90°C. 80.5 g of phosphorus oxychloride (525 mmol) are added dropwise thereto at from 90 to 103°C, and the reaction mixture is heated at 110°C for 2 hours. After cooling to 20°C, the reaction mixture is adjusted to pH 8 using 4M sodium

hydroxide solution, with cooling. The aqueous phase is separated off and extracted with 100 ml of toluene. The combined organic phases are washed three times with 100 ml of water each time and dried at RT under 2 mbar. 89.7 g (105 %; contains toluene) are obtained.

Example 9: Preparation of 4-dodecylamino-2-isopropyl-6-methylpyrimidine (compound of formula (93))

79.2 g of 4-chloro-2-isopropyl-6-methylpyrimidine (464.1 mmol) are heated in 100 ml of dioxane at 100°C. A heated solution of 189.3 g of dodecylamine (1021 mmol, 2.2 eq) in 30 ml of dioxane is added dropwise thereto over the course of 2 hours, and the reaction mixture is further heated for 2 hours at 100°C and for 9 hours at 109°C. After cooling, 400 ml of ethyl acetate and 150 ml of 4M sodium hydroxide solution (600 mmol) are added thereto and the mixture is stirred at 50°C for 10 minutes. The lower, aqueous phase is discarded, the organic phase is washed with 300 ml of water, and 10 ml of saturated NaCl solution are added thereto. The organic phase is separated off and concentrated, and the excess dodecylamine is distilled *in vacuo* up to a bath temperature of 160°C.
136.1 g (91.8 %); GC purity: 98 %

NMR 1H (ppm in $CDCl_3$): 0.7,t,3H; 1.1, m, 24H; 1.4, m, 2H; 2.15, s, 3H; 2.75,Q, 1H; 3.05, m, 2H; 4.9, s, 1H; 5.8, s, 1H

Example 10: Determination of the minimum inhibitory concentration (MIC value) in microtitre plates

Nutrient medium:

Casein/soymeal peptone broth for preparation of pre-cultures of test bacteria and yeast.

Examples of test organisms:

Bacteria: Pseudomonas aeruginosa CIP A-22 (=PA)
Escherichia coli NCTC 8196 (= EC)
Staphylococcus aureus ATCC 9144 (= SA)
Candida albicans ATCC 10231 (= CA)

Procedure:

The test substances are pre-dissolved in dimethyl sulfoxide (DMSO) and tested in a dilution series of 1:2.

Bacteria and yeast are cultured overnight in CASO broth.

All the test organism suspensions are adjusted to an organism count of 1 - 5 x 10^8 CFU/ml using 0.85 % sodium chloride solution.

The test substances are pre-pipetted into microtitre plates in amounts of 8 µl per well.

The pre-adjusted organism suspensions are diluted 1:100 in CASO broth and are added in amounts of 192 µl per well to the test substances.

The test batches are incubated for 48 hours at 37°C.

After incubation, the growth is determined on the basis of the turbidity of the test batches (optical density) at 620 nm in a microplate reader.

The minimum inhibitory concentration (MIC value) is the concentration of substance at which (compared to the growth of the control) an appreciable inhibition of growth (≤ 20 % growth) of the test organisms is observed.

Three microtitre plates are used for each test organism and substance concentration. All the substances are tested in duplicate.

The microbiological test results are compiled in Table 2:

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
3	64	72	7.5	15	>120	7.5
4	37	96	7.5	30	>120	15
5	83	97	7.5	>120	>120	>120

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
6	92	97	7.5	60	>120	>120
7	43	48	15	15	>120	30
8	82	93	30	30	>120	120
9	94	98	15	15	>120	30
10	49	59	15	30	>120	30
11	75	89	7.5	15	>120	7.5
12	95	97	7.5	3.75	7.5	7.5
13	94	99	15	15	>120	30
14	91	97	15	3.75	30	15
15	91	98	15	>120	>120	>120
16	42	44	7.5	15	>120	15
17	39	43	15	30	>120	15
18	42	51	30	30	120	60
19	64	70	7.5	15	>120	8
20	63	77	15	30	>120	15
21	70	82	7.5	<3.75	7.5	<3.75
22	51	65	15	15	>120	7.5
23	67	82	15	7.5	30	7.5
24	95	97	30	15	30	30
25	88	96	>120	60	>120	120
26	81	90	60	60	>120	>120
27	88	93	30	30	>120	60
28	86	93	<3.75	>120	>120	>120
29	61	62	15	30	>120	30
30	85	72	60	30	>120	15
31	45	42	60	>120	>120	120
32	69	64	60	120	>120	60
33	94	93	30	>120	>120	60
34	89	89	7.5	120	>120	30

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
35	92	88	15	30	120	30
36	82	73	7.5	15	60	7.5
37	82	66	7.5	15	>120	7.5
38	56	34	<3.75	7.5	>120	<3.75
39	67	46	<3.75	30	>120	15
40	43	44	60	>120	>120	120
41	81	77	30	>120	>120	60
42	91	92	<3.75	120	>120	30
43	72	68	60	>120	>120	120
44	88	84	120	>120	>120	120
45	82	83	60	>120	>120	120
46	88	88	120	>120	>120	120
47	72	67	120	>120	>120	>120
48	81	85	30	>120	>120	60
49	92	84	120	>120	>120	>120
50	84	86	120	>120	>120	>120
51	77	73	30	>120	>120	>120
52	88	91	30	>120	>120	120
53	87	89	60	>120	>120	120
54	90	91	15	>120	>120	120
55	85	87	120	>120	>120	>120
56	87	84	60	>120	>120	120
57	99	99	60	>120	>120	120
58	58	78	15	120	>120	60
59	34	64	15	60	>120	60
60	46	32	120	>120	>120	120
61	90	87	30	120	>120	120
62	66	61	60	120	>120	120
63	99	95	15	30	>120	60

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
64	80	80	7.5	30	>120	15
65	96	92	30	60	>120	15
66	90	95	<3.75	30	>120	30
67	48	44	7.5	30	>120	7.5
68	37	38	15	30	>120	15
69	64	79	<3.75	30	>120	7.5
70	71	82	<3.75	15	>120	7.5
71	88	88	7.5	15	>120	7.5
72	79	52	7.5	15	>120	7.5
73	90	96	<3.75	7.5	>120	<3.75
74	79	39	<3.75	7.5	>120	<3.75
75	92	89	7.5	15	>120	7.5
76	97	95	15	60	>120	30
77	86	90	7.5	60	>120	15
78	90	94	<3.75	7.5	>120	<3.75
79	92	95	<3.75	<3.75	>120	<3.75
80	54	50	<3.75	7.5	>120	7.5
81	40	42	<3.75	<3.75	>120	<3.75
82	67	84	<3.75	15	>120	7.5
83	77	72	<3.75	7.5	>120	<3.75
84	93	91	15	15	>120	7.5
85	83	80	15	7.5	>120	7.5
86	92	92	15	15	>120	7.5
87	95	94	15	15	>120	7.5
88	95	94	15	15	>120	7.5
89	92	90	<3.75	<3.75	>120	<3.75
90	54	33	7.5	15	>120	<3.75
91	89	95	30	30	>120	15
92	52	48	<3.75	15	>120	7.5

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
93	40	39	<3.75	15	>120	7.5
94	65	80	<3.75	15	>120	7.5
95	82	83	15	30	>120	15
96	78	85	15	30	>120	15
97	31	26	7.5	15	>120	15
98	79	60	15	15	>120	15
99	93	90	15	15	>120	30
100	71	59	15	15	>120	15
101	87	78	7.5	7.5	>120	7.5
102	49	25	7.5	30	>120	15
103	89	89	15	60	>120	30
104	54	41	<3.75	7.5	>120	7.5
105	33	38	7.5	15	>120	7.5
106	65	75	<3.75	15	>120	15
107	80	82	7.5	15	>120	15
108	87	96	30	>120	>120	>120
109	87	87	15	60	>120	30
110	90	94	60	>120	>120	120
111	94	92	7.5	120	>120	60
112	87	90	15	120	>120	30
113	92	85	7.5	120	>120	30
114	41	28	15	>120	>120	30
115	93	96	7.5	>120	>120	120
116	58	46	7.5	60	>120	15
117	39	40	15	120	>120	30
118	54	70	7.5	60	>120	15
119	82	87	7.5	>120	>120	120
120	42	35	30	120	>120	30
121	87	90	30	>120	>120	>120

Table 2:

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC PA	MIC CA
122	78	87	30	>120	>120	120
123	68	73	120	>120	>120	>120
124	93	96	60	120	>120	60
125	93	93	120	>120	>120	120
126	87	86	120	>120	>120	120
127	65	69	60	>120	>120	60
128	46	52	120	>120	>120	120
129	58	69	120	>120	>120	120
130	82	83	120	>120	>120	>120
131	73	74	120	>120	>120	>120
132	88	90	60	>120	>120	>120
133	94	93	15	>120	>120	>120
134	100	89	7.5	>120	>120	120
135	92	91	60	120	>120	30
136	92	92	7.5	>120	>120	60
137	49	44	15	30	>120	15
138	41	41	30	60	>120	30
139	50	66	7.5	60	>120	30
140	100	80	15	>120	>120	120
141	74	71	120	>120	>120	>120
142	100	83	30	>120	>120	120
143	84	79	>120	>120	>120	120
144	62	54	60	>120	>120	120
145	43	39	>120	>120	>120	120
146	34	35	>120	>120	>120	120
147	61	73	60	>120	>120	120
148	72	70	120	>120	>120	>120

Example 11: Agar incorporation test CG128e

Medium: Casein/soymeal peptone agar (Merck)
*Sabouraud 4 % glucose agar (Merck)

Diluent: Sterile 0.85 % NaCl solution

Incubation: 24 hours at 37°C
*3 days at 28°C

Test solution: 1 % stock solutions of all the test substances are prepared in a suitable solvent and diluted in serial dilutions to end concentrations of from 1000 ppm to 10 ppm.

Test principle:

0.3 ml of each dilution step is mixed with 15 ml of nutrient medium while the latter is still liquid. After the nutrient medium has solidified, 10 µl of each of the following organism dilutions of the test strains in 0.85 % NaCl solution are spotted onto the agar medium:

Microorganisms used:

Staphylococcus aureus ATCC 6538	Staphylococcus aureus ATCC 9144
Staphylococcus epidermidis ATCC 12228	Corynebacterium xerosis * ATCC 373
C. minutissimum ATCC 23348	Propionibacterium acnes (*) ATCC 6919
Escherichia coli NCTC 8196	Escherichia coli ATCC 10536
Proteus vulgaris ATCC 6896	Klebsiella pneumoniae ATCC 4352
Salmonella choleraesuis ATCC 9184	Pseudomonas aeruginosa ATCC 15442
Candida albicans ATCC 10231	Aspergillus niger ATCC 6275

The plates are incubated at 37°C for 24 hours (A. niger at 28°C for 3 days) and then the highest dilution (lowest concentration) of the test substance at which growth is just no longer discernible (corresponds to the MIC) is determined.
The results are shown in Table 3.

Table 3:

	Compound of formula		
Microorganism	(36)	(89)	(93)
Staphylococcus aureus ATCC 6538	120	7.5	3.75
Staphylococcus aureus ATCC 9144	120	7.5	3.75
Staphylococcus epidermidis ATCC 12228	> 120	120	3.75
Corynebacterium xerosis * ATCC 373	60	3.75	1.88 *
C. minutissimum ATCC 23348	30	3.75	1.88
Propionibacterium acnes (*) ATCC 6919	60	3.75	3.75 (*)
Escherichia coli NCTC 8196	120	120	120
Escherichia coli ATCC 10536	> 120	> 120	120
Proteus vulgaris ATCC 6896	> 120	60	> 120
Klebsiella pneumoniae ATCC 4352	60 **	> 120	60
Salmonella choleraesuis ATCC 9184	> 120	> 120	120
Pseudomonas aeruginosa ATCC 15442	> 120	> 120	> 120
Candida albicans ATCC 10231	> 120	> 120	> 120
Aspergillus niger ATCC 6275	> 120	> 120	> 120

Example 12: "Microbicidal activity" suspension test CG 161/EN1040

Test method:

Nutrient medium:

Casein/soymeal peptone broth for preparation of pre-cultures of test bacteria

Examples of test organisms:

Staphylococcus aureus ATCC 6538

Escherichia coli ATCC 10536

Actynomyces viscosus ATCC 43146

Procedure:

The test substances are dissolved in dimethyl sulfoxide (DMSO) and tested in a concentration of 120 µg/ml.

Bacteria are incubated overnight in CASO broth and adjusted to an organism count of 1 - 5 x 10^5 CFU/ml using 0.85 % sodium chloride solution.

The test substances are pre-pipetted into microtitre plates in amounts of 8 µl per well.

The adjusted test organism suspensions are added in amounts of 192 µl per well to the test substances and mixed. After defined contact times, the test batches are mixed, an aliquot is withdrawn and diluted in several steps in a dilution series of 1:10 in a suitable inactivation medium.

The test plates are incubated for 24 hours at 37°C. After incubation, the growth is determined on the basis of the turbidity of the test batches (optical density) at 620 nm in a microplate reader.

On the basis of the number of steps in the dilution series that exhibit growth, the reduction in the test organism concentration is determined in powers of ten (log value).

One microtitre plate is used for each test organism.

All the substances are tested in duplicate.

The results (log reduction) are shown in Table 4:

Table 4

		Compound of formula			
Organism	Contact time	(93) 0.12 %	(93) 120 ppm	(89) 0.12 %	(89) 120 ppm
S.aureus	5 min	>5	1.4		<1
S.aureus	30 min	>5	3.8		1.7
E. coli	5 min	>5	>5		4.6
E. coli	30 min	>5	>5		>5

Table 4					
		Compound of formula			
Organism	Contact time	(93) 0.12 %	(93) 120 ppm	(89) 0.12 %	(89) 120 ppm
A. viscosus	5 min	>5	2	4.9	3.9
A. viscosus	30 min	>5	4	>5	4.3

Example 13: Determination of the minimum inhibitory concentration (MIC value) in microtitre plates

Nutrient medium and test procedure correspond to Example 10.

As test organisms there are used:

Staphylococcus aureus ATCC 6538

Escherichia coli ATCC 10536

Actynomyces viscosus ATCC 43146

The microbiological test results are compiled in Table 5:

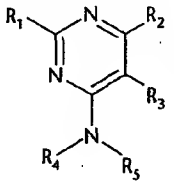
Table 5					
Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC AV
149	91	89	120	>120	15
150	87	88	120	>120	60
151	88	86	120	>120	15
152	91	83	30	>120	15
153	89	85	120	>120	30
154	94	85	120	120	30
155	85	81	30	30	7.5
156	86	82	7.5	15	<3.75
157	62	63	15	>120	<3.75
158	86	92	>120	>120	7.5
159	89	91	120	>120	30
160	88	92	120	>120	15

Table 5

Comp. of formula	Purity [%] 254 nm	Purity [%] 280 nm	MIC SA	MIC EC	MIC AV
161	87	92	120	>120	30
162	67	88	120	>120	30
163	67	66	>120	>120	60
164	85	92	120	>120	30
165	81	92	>120	>120	30
166	68	75	>120	>120	30
167	92	89	120	120	15
168	72	73	>120	>120	15
169	87	83	>120	>120	30
170	77	85	>120	>120	15
171	86	81	120	>120	30
172	87	72	60	>120	15
173	69	67	60	60	15
174	66	87	120	>120	60
175	69	64	120	120	30
176	82	57	30	30	7.5
177	87	92	120	>120	30
178	77	69	120	120	30
179	77	85	120	120	30

What is claimed is:

1. Use of a 4-aminopyrimidine of formula

(1)  , wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms; biphenyl or C_6-C_{10}aryl which is unsubstituted or substituted by halogen, C_1-C_3alkyl, C_1-C_3alkoxy or by amino; a 5- to 7-membered heteroaryl radical; or cyclo-C_3-C_7alkyl;

R_3 is hydrogen; phenyl or C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms;

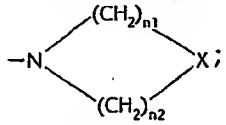
R_4 is hydrogen; C_1-C_{10}alkyl; phenyl; or a 5- to 7-membered heteroaryl radical;

R_5 is C_1-C_{20}alkyl which is unsubstituted or substituted by one or more halogen atoms or by a heterocyclic radical or interrupted by one or more –O- or  groups or by a

bivalent heterocyclic radical; NR''R'''-C_1-C_{20}alkyl which is unsubstituted or substituted by a heterocyclic radical or interrupted by one or more –O- or  groups or by a

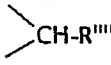
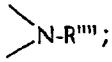
bivalent heterocyclic radical; cyclo-C_5-C_8alkyl; hydroxy-C_1-C_{20}alkyl; phenyl-C_1-C_3alkyl; a heterocyclic radical; or

R_4 and R_5, together with the nitrogen atom linking them, form a radical of

formula (1a)  ;

R' is hydrogen; or C_1-C_3alkyl;

R'' and R''' are each independently of the other hydrogen; C_1-C_5alkyl; or hydroxy-C_1-C_5alkyl;

X is  ;  ; or  ;

R'''' is hydrogen; C_1-C_4alkyl; or heteroaryl-C_1-C_4alkyl; and

n_1 and n_2 are each independently of the other from 1 to 8;

in the antimicrobial treatment of surfaces.

2. Use according to claim 1, wherein

R_5 is R"R'"N-C_1-C_{20}alkyl which is uninterrupted or interrupted by one or more –O- or

groups or by a bivalent heterocyclic radical;

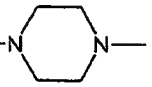
R' is hydrogen; or C_1-C_5alkyl;

R" and R'" are each independently of the other hydrogen; or methyl;

and

R_1, R_2, R_3 and R_4 are as defined in claim 1.

3. Use according to either claim 1 or claim 2, wherein

R_5 is R"R'"N-C_1-C_{20}alkyl which is uninterrupted or interrupted by  .

4. Use according to either claim 1 or claim 2, wherein

R_5 is R"R'"N-C_5-C_{20}alkyl which is uninterrupted or interrupted by one or more –O- or

groups;

R' is hydrogen; or C_1-C_5alkyl; and

R" and R'" are each independently of the other hydrogen; or methyl.

5. Use according to claim 4, wherein

R_5 is R"R'"N-C_5-C_{20}alkyl; and

R" and R'" are each independently of the other hydrogen; or methyl.

6. Use according to claim 1, wherein

R_4 is hydrogen; or C_1-C_5alkyl;

R_5 is C_5-C_{20}alkyl which is unsubstituted or interrupted by –NH-; and

R_1, R_2 and R_3 are as defined in claim 1.

7. Use according to claim 6, wherein

R_1 is hydrogen; C_1-C_5alkyl; unsubstituted or C_1-C_4alkyl-substituted phenyl or phenyl-C_1-C_4alkyl; or pyridino;

R_2 is hydrogen; or C_1-C_5alkyl; especially methyl;

R_3 is hydrogen; or C_1-C_5alkyl;

R_4 is hydrogen; or C_1-C_5alkyl; and

R_5 is C_5-C_{20}alkyl.

8. Use according to either claim 6 or claim 7, wherein

R_1 is hydrogen; C_1-C_5alkyl, especially isopropyl or methyl; unsubstituted or C_1-C_4alkyl-substituted phenyl; or pyridino;

R_2 is methyl;

R_3 and R_4 are hydrogen; and

R_5 is C_8-C_{18}alkyl.

9. Use according to any one of claims 6 to 8, wherein

R_5 is linear C_8-C_{18}alkyl.

10. Use according to claim 1, wherein, in formula (1a),

R'''' is hydrogen; or pyridyl-C_1-C_3alkyl; and

n_1 and n_2 are in each case 2.

11. Use according to any one of claims 1 to 8, wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl; phenyl which is unsubstituted or substituted by halogen, C_1-C_5alkyl, C_1-C_5alkoxy or by amino; biphenyl; cyclo-C_3-C_7alkyl; 3-pyridyl; 4-pyridyl; 2-thiophenyl; 3-thiophenyl; or thiazolyl.

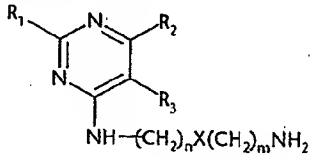
12. Use according to any one of claims 1 to 6, wherein

R_3 is hydrogen; or phenyl.

13. Use according to any one of claims 1 to 10, wherein

R_4 is hydrogen.

14. Use according to claim 1, relating to compounds of formula

(2) 

wherein

X is -O-; or —N(R')— ;

R' is hydrogen; or C_1-C_3alkyl;

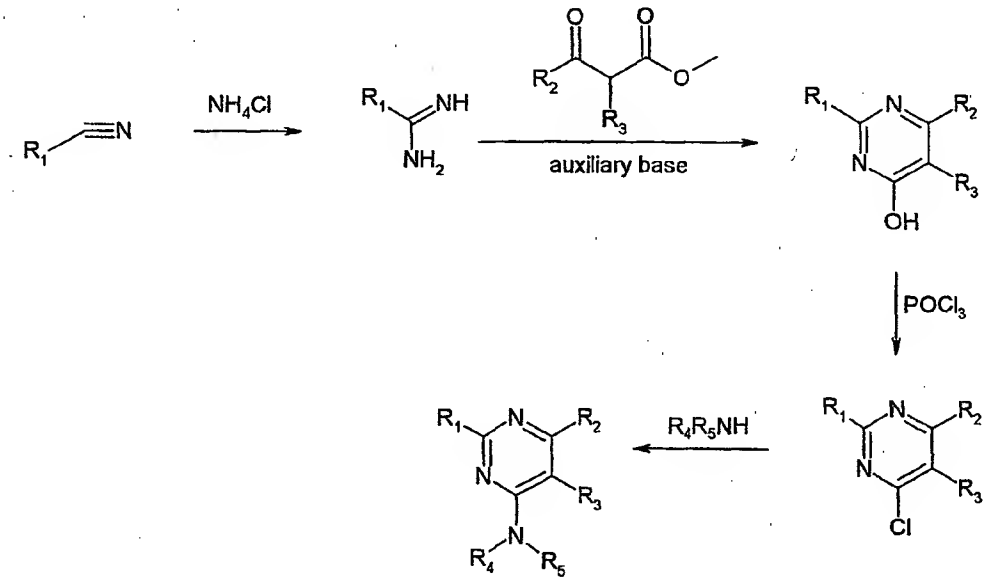
n is 1-3; and

m is 1-3;

and

R_1, R_2 and R_3 are as defined in claim 1.

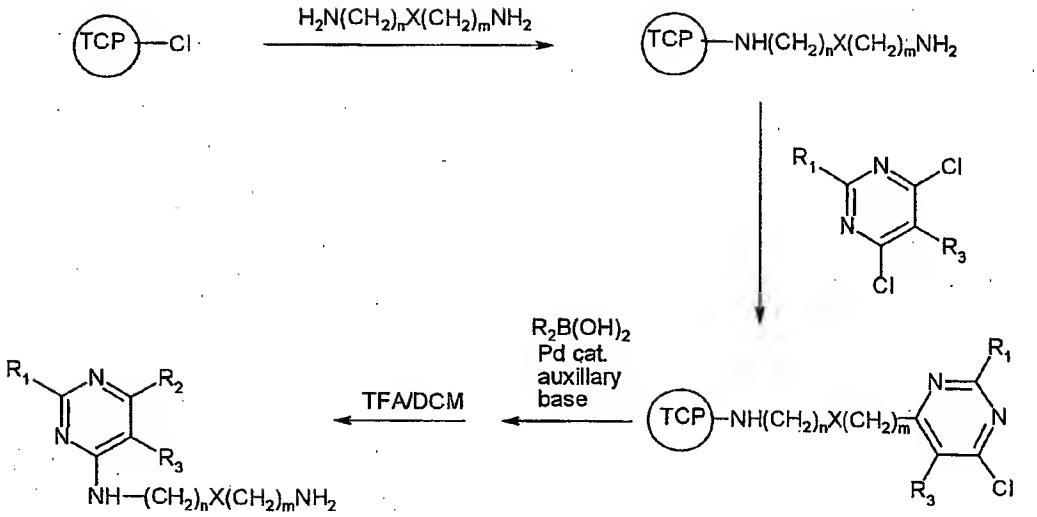
15. A process for the preparation of a compound of formula (1), which comprises reacting 2-amidinopyridine with a keto ester using an auxiliary base in a suitable solvent in accordance with the following scheme:



wherein

R_1, R_2, R_3, R_4 and R_5 are as defined in claim 1.

16. A process for the preparation of a compound of formula (2), which comprises preparing the compound in a solid-phase synthesis using a trityl (TCP) resin in accordance with the following scheme :



wherein

R_1, R_2, R_3, X, m and n are as defined in claim 14.

17. Use according to claim 1, wherein the compound of formula (1) is used in the antimicrobial treatment, deodorisation and disinfection of the skin, mucosa and hair.

18. Use according to claim 1, wherein the compound of formula (1) is used in the treatment of textile fibre materials.

19. Use according to claim 1, wherein the compound of formula (1) is used in preservation.

20. Use according to claim 1, wherein the compound of formula (1) is used in washing and cleaning formulations.

21. Use according to claim 1, wherein the compound of formula (1) is used in imparting antimicrobial properties to, and preserving, plastics, paper, nonwovens, wood or leather.

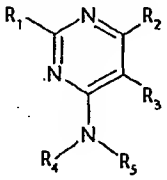
22. Use of a compound of formula (1) in imparting antimicrobial properties to, and preserving, technical products, especially printing thickeners of starch or of cellulose derivatives, surface-coatings and paints.

23. Use of a compound of formula (1) as a biocide in technical processes.

24. A personal care preparation comprising
from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formula (1), and cosmetically tolerable adjuvants.

25. An oral composition comprising from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formula (1), and orally tolerable adjuvants.

26. A compound of formula

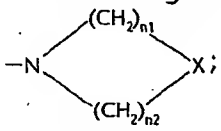
(1')  wherein

R_1 and R_2 are each independently of the other hydrogen; C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms; biphenyl or C_6-C_{10}aryl which is unsubstituted or substituted by halogen, C_1-C_5alkyl, C_1-C_5alkoxy or by amino; a 5- to 7-membered heteroaryl radical; or cyclo-C_3-C_7alkyl;

R_3 is hydrogen; phenyl or C_1-C_5alkyl which is unsubstituted or substituted by one or more halogen atoms;

R_4 is hydrogen; C_1-C_{10}alkyl; phenyl; or a 5- to 7-membered heteroaryl radical;

R_5 is C_1-C_{20}alkyl which is unsubstituted or substituted by one or more halogen atoms or by a heterocyclic radical or interrupted by one or more –O- or groups or by a bivalent heterocyclic radical; $NR''R'''$-C_1-C_{20}alkyl which is unsubstituted or substituted by a heterocyclic radical or interrupted by one or more –O- or groups or by a bivalent heterocyclic radical; cyclo-C_5-C_8alkyl; hydroxy-C_1-C_{20}alkyl; phenyl-C_1-C_3alkyl; a heterocyclic radical; or

R_4 and R_5, together with the nitrogen atom linking them, form a radical of formula (1a)  ;

R' is hydrogen; or C_1-C_3alkyl;

R'' and R''' are each independently of the other hydrogen; C_1-C_5alkyl; or hydroxy-C_1-C_5alkyl;

X is $>O$; $>CH\text{-}R''''$; or $>N\text{-}R''''$;

R'''' is hydrogen; C_1-C_4alkyl; or heteroaryl-C_1-C_4alkyl; and

n_1 and n_2 are each independently of the other from 1 to 8;

not including compounds of formula (1') wherein simultaneously

R_1 is C_6-C_{10}aryl; or C_1-C_4alkyl; and

R_5 is C_1-C_7alkyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02438

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N43/54 A01N43/78 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 323 757 A (UBE INDUSTRIES) 12 July 1989 (1989-07-12) page 3, line 26 -page 5, line 12 table 1 ---	1,6-9, 11-13, 17-25
X	EP 0 407 899 A (HOECHST AG) 16 January 1991 (1991-01-16) page 2, line 1 -page 4, line 38 table A ---	1,6-10, 12,13, 17-25
X	EP 0 519 211 A (HOECHST AG) 23 December 1992 (1992-12-23) page 3, line 1 - line 3 table A --- -/--	1,6-9, 11-13, 17-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2003	09.07.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fort, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02438

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 07278 A (DU PONT DE NEMOURS) 16 March 1995 (1995-03-16) * the whole document *	1,6-9, 11-13, 17-25
X	US 6 207 668 B1 (RALF BRAUN ET AL.) 27 March 2001 (2001-03-27) * the whole document *	1,10-13, 17-25
X	EP 0 424 125 A (UBE INDUSTRIES) 24 September 1991 (1991-09-24) * the whole document *	1,11-13, 17-25
X	US 4 435 402 A (HIDEAKARA TSUJI ET AL.) 6 March 1984 (1984-03-06) column 1, line 24 -column 4, line 58	1,11,13, 17-25

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14, 17-25

   Use of 4-aminopyrimidine of formula (1) in the antimicrobial treatment of surfaces and corresponding personal care preparation and oral composition

2. Claim : 15

   Process for the preparation of a compound of a compound of formula (1) which comprises reacting an amidine compound with a keto ester

3. Claim : 16

   Process for the preparation of a compound of formula (2) using a trityl (TCP) resin

4. Claim : 26

   A compound of formula (1') not including compounds of formula (1') wherein simultaneously
   R1 is C6-C10 aryl; or C1-C4 alkyl; and
   R5 is C1-C7 alkyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02438

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14,17-25

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/02438

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0323757	A	12-07-1989	CA	1337525 C	07-11-1995
			DE	3853771 D1	14-06-1995
			DE	3853771 T2	05-10-1995
			EP	0323757 A2	12-07-1989
			JP	2007331 C	11-01-1996
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